Adverse Nephrotoxic Events in Critically Ill Children: A Pharmacoepidemiologic Evaluation

by

Morgan Brooke Slater

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Science
University of Toronto

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Doctor of Philosophy
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2014

Abstract

**Background:** Kidney injury is a common adverse event in critically ill children and has a complex and multifactorial etiology. Some factors, such as age and sex, are non-modifiable while others, including medication exposure, are modifiable and present an opportunity to decrease the risk of kidney injury. The objective of this dissertation was to quantify the risk of acute kidney injury (AKI) attributable to the initiation of nephrotoxic medications among critically ill children.

**Methods:** We utilized a pharmacoepidemiologic approach, using AKI as a model for studying adverse drug events (ADEs) in children. First, we conducted a systematic review of the application of an accepted definition of AKI (the RIFLE criteria) in children. Second, we estimated the incidence and associated factors of AKI in a 3.5-year cohort of critically ill children. Finally, we conducted a nested case-control study to quantify the risk of developing AKI after the initiation of one or more nephrotoxic medications.

**Results:** Our systematic review identified wide variation in the application of the RIFLE. We found an AKI incidence of 23.7% in our patient population and identified patients at
increased risk for the development of AKI. Administration of nephrotoxic medications during ICU admission was the single greatest risk factor for AKI. We found a high incidence of nephrotoxic medication use in the ICU; over 80% of patients were exposed to one or more nephrotoxic medications. The administration of ganciclovir, furosemide and gentamicin were significantly associated with increased odds of developing AKI before and after adjustment for underlying differences in risk factors of AKI.

**Conclusion:** Acute kidney injury is common among critically ill children. Nephrotoxic medication exposure preceding AKI is common. The results of this work can help to optimize prescribing and aid clinicians in making optimal treatment choices, reducing harm and improving patient outcomes.
Acknowledgments

I would like to extend many thanks and appreciate to all those who have encouraged and supported me during the course of my graduate studies. First, to my supervisor, Dr. Christopher Parshuram: thank you for your continued support and guidance. My committee members, Dr. Andrew Howard, Dr. Gideon Koren and Dr. Paula Rochon, were instrumental in my research and I thank them for their guidance, insight, encouragement and support during this long process. Andrew Howard is owed a special mention: he hired me after I completed my MSc degree and gave me my first opportunity in clinical research. Along the years he has always been supportive of my career and I am fortunate to call him a mentor. Dr. Andrea Gruneir, an informal member of my thesis committee, provided much wisdom, methodological expertise and insight into the arduous process of completing a doctoral degree.

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I am fortunate to call Dr. Valeria Rac both a friend and a mentor. Her time, support, advocacy and expertise have been priceless and her love and enthusiasm for her work is an example for me. She has been unwavering in her support and without her, this thesis would not have been possible. She is a brilliant scientist and I can only aspire to be half as talented as she is.

During my career, I have been involved with a number of research groups across the spectrum of health care priorities. All of these experiences have helped to shape how I think
about research. Two people stand out to me: I owe special thanks to both Dr. Dorcas Beaton and Dr. Rick Glazier. Both are amazing people and dedicated researchers who have helped shaped my career goals.

Above all, I am fortunate to have family and friends who have listened to me throughout this long, long process. To you all, words cannot express my thanks for your love, support and patience.

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Finally, this thesis is dedicated to my Nono, Aldo Narduzzi, who instilled the importance of education and life-long learning in me from a very young age. I hope he is proud.
Contributions

I, Morgan Slater, solely prepared this thesis and am the first author of the three manuscripts directly resulting from this thesis work. All aspects of this work, including the planning, execution, analysis and writing of all original research and publications, were performed by the primary author. The following contributions by other individuals are formally acknowledged:

Dr. Christopher Parshuram, Dr. Andrew Howard, Dr. Gideon Koren, Dr. Paula Rochon and Dr. Andrea Gruneir all provided mentorship, guidance and assistance in the planning and execution of the analyses and manuscript/thesis preparation.

Dr. Vijay Anand was the second reviewer for the systematic review (Chapter 3). He also assisted with the editing of the resulting manuscript.

Elizabeth Uleryk provided expertise and guidance in conducting the literature search for the systematic review (Chapter 3). She also assisted with the editing of the resulting manuscript.

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<th>Full Form</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>AKIN</td>
<td>Acute Kidney Injury Network</td>
</tr>
<tr>
<td>ARF</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>ATN</td>
<td>Acute tubular necrosis</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CICU</td>
<td>Cardiac intensive care unit</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CYP450</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>eCCI</td>
<td>Estimated creatinine clearance</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
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<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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<tr>
<td>FeNa</td>
<td>Fractional excretion of sodium</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>HSC</td>
<td>Hospital for Sick Children</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IL-18</td>
<td>Interleukin-18</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
</tr>
<tr>
<td>KIM-1</td>
<td>Kidney injury molecule-1</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of diet in renal disease</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple organ dysfunction syndrome</td>
</tr>
<tr>
<td>NGAL</td>
<td>Neutrophil gelatinase-associated lipocalin</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PELOD</td>
<td>Paediatric logistic organ dysfunction</td>
</tr>
<tr>
<td>PICU</td>
<td>Paediatric intensive care unit</td>
</tr>
<tr>
<td>PIM2</td>
<td>Paediatric index of mortality</td>
</tr>
</tbody>
</table>
pRIFLE  Paediatric RIFLE (Risk, injury, failure, loss of kidney function, and end-stage kidney disease)

PRISM  Pediatric risk of mortality

RACHS-1  Risk adjustment in congenital heart surgery

RIFLE  Risk, injury, failure, loss of kidney function, and end-stage kidney disease

ROP  Retinopathy of prematurity

RRT  Renal replacement therapy

SCr  Serum creatinine

SIRS  Systemic inflammatory response syndrome

TBSA  Total body surface area

UO  Urine output

VIF  Variance inflation factor
Chapter 1  Overview
1.1 Preamble

Kidney injury is a common adverse event in critically ill children. The etiology of acute kidney injury (AKI) is complex and multifactorial; some factors, such as age and sex are non-modifiable while others, including exposure to medications, are controllable and present the opportunity to decrease the risk of AKI.

The complexity of AKI is magnified in the critical care unit, where patients are acutely ill and it can be difficult for clinicians to distinguish drug from disease-related causes of AKI. The goal of this thesis project was to evaluate the contribution of drug therapy to acute kidney injury (AKI), a common adverse event in critically ill children. To identify patients with AKI, we chose to utilize a consensus definition known as the RIFLE. The rationale for this decision will be presented in Chapter 2. First, we needed to understand how RIFLE-defined AKI is operationalized in the literature. This informed how we operationalized the definition of AKI in the remainder of the thesis work. We then needed to quantify characteristics and clinical factors that place patients at higher risk for developing AKI. Finally, combining these results, we then evaluated the association between specific medications and the development of AKI, controlling for underlying differences in risk.

The results of this dissertation will add to the growing literature of AKI in critically ill children. Through understanding what factors and medications increase the risk of AKI, we can optimize prescribing and help clinicians make optimal treatment choices, thus reducing harm and improving outcomes.
1.2 Research Objectives

The aim of this thesis work was to evaluate the contribution of drug therapy to acute kidney injury. The specific research objectives of this thesis were to:

1. Systematically evaluate the published literature describing the use of the RIFLE definition of acute kidney injury in children;

2. Determine the clinical risk factors of acute kidney injury in critically ill children; and

3. Evaluate the contribution of drug therapy to the development of acute kidney injury.

Each research objective above corresponds to a specific chapter in the thesis work.

1.3 Thesis Organization

This thesis has been written following a three-paper approach. This chapter provides an overview of the thesis, states the specific research aims and presents the overall organization of the thesis. Chapter 2 provides the rationale and context for this work, introducing concepts of acute kidney injury and nephrotoxicity at a macro level. The three specific research aims stated above are answered through separate studies and are presented in Chapters 3, 4 and 5, respectively. Finally, Chapter 6 summarizes the major research findings and implications of this research, as well as discusses the opportunities for future study.

The contents of Chapter 3 have been published in *Kidney International*. The contents of Chapters 4 and 5 are currently under review at *Kidney International* and *Critical Care Medicine*, respectively.
respectively. The formatting of these published or submitted manuscripts has been adapted to conform to this thesis. A common reference section for all chapters follows Chapter 6.
Chapter 2    Acute Kidney Injury, Adverse Drug Events and Nephrotoxicity
2.1 Overview

The purpose of this chapter is to provide context for the rationale of the thesis work by reviewing concepts of acute kidney injury (AKI) and nephrotoxicity.

The etiology, incidence and outcomes of acute kidney injury are outlined, followed by a description of current definition of AKI. This provides the rationale for the choice of AKI definition used throughout the remainder of the thesis work. Following this is a discussion of adverse drug events, including definition, incidence and outcomes. We provide information regarding two high-risk populations, critically ill and paediatric patient populations, the focus of this thesis. Finally, we discuss common adverse drug events in children and the importance of increasing drug safety knowledge in paediatric populations.

The chapter then introduces nephrotoxicity as an important cause of acute kidney injury and briefly discusses the mechanisms of injury. It should be noted that a detailed description of acute kidney injury at the cellular level is beyond the scope of this thesis work. Finally, we discuss methods of studying drug safety in children and present pharmacoepidemiology as a viable method to study nephrotoxicity, as a model to study adverse drug events, in children.

2.2 Acute Kidney Injury

The kidneys are an essential organ; their main functions include the removal of waste products from the blood, the regulation of sodium, potassium and other electrolytes, the regulation of fluid balances and blood pressure, the maintenance of acid-base balance, and the production of various
hormones. The function unit of the kidney is the nephron, composed of a filtering unit called the glomerulus and its associated renal tubule (Figure 2.1). Each kidney is comprised of roughly one million nephrons. Arterial blood enters the kidney via the renal artery. Blood entering the glomerulus is filtered across the fenestrated glomerular capillary wall, producing an ultrafiltrate that crossed into Bowman’s space and then enters the tubular lumen proper. As this ultrafiltrate traverses the length of the tubule, its composition is modified by reabsorption and secretion of specific components by the tubular epithelial cells. The end result of this process is the formation of urine, which is transported to the bladder via the ureters, and the concomitant return of cleaned blood to the circulation through the renal vein ("Urinary System" 2002).
Figure 2.1: Kidney anatomy and physiology

As blood passes through the kidneys from the renal artery to the renal vein, waste is collected and turned into urine. Inside each kidney is a network of small tubes (nephrons) which filter blood. Waste products in the nephrons move from the capillaries into the urine collecting tubes and into the ureter to the bladder from the renal pelvis, located in the centre of each kidney.


Acute kidney injury (AKI) is defined as an abrupt deterioration in kidney function, which results in an accumulation of creatinine, urea and other waste products (Bellomo, Kellum, & Ronco, 2012; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; "Renal Failure," 2006). The severity spectrum of AKI is broad, starting with patients who are at risk for AKI, due to genetic or clinical risk factors, proceeding to renal injury or dysfunction, and culminating in acute renal failure (ARF) (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). It can present as subtle
biochemical and structural changes, minimal elevations in serum creatinine, or anuric renal failure (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). AKI is a common comorbid condition in critically ill children and adults (Basu, Devarajan, Wong, & Wheeler, 2011; Ricci, Cruz, & Ronco, 2008) and independently predicts mortality in these patient populations (Akcan-Arikan et al., 2007; D. J. Askenazi, Griffin, McGwin, Carlo, & Ambalavanan, 2009; Ricci et al., 2008; Zappitelli et al., 2008).

Any degree of kidney injury has significant implications on patient health; even mild, reversible AKI has important clinical consequences including increased mortality (Eric A. J. Hoste et al., 2006; Shigehiko Uchino, Bellomo, Goldsmith, Bates, & Ronco, 2006). Unfortunately, mild injury to the renal system begins long before the loss of kidney function can be measured with standard tests (Bellomo et al., 2012; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012).

### 2.2.1 Etiology of AKI

The etiology of AKI has changed over the past decade from primary renal disease to complications of other systemic illness (D. Askenazi, 2011; Hui-Stickle, Brewer, & Goldstein, 2005; Symons et al., 2007). In critically ill patients, AKI is commonly multifactorial, resulting from conditions including hypotension, sepsis, congenital heart disease, ischemic injury, nephrotoxins or malignancy (Akcan-Arikan et al., 2007; Duzova et al., 2010; Hui-Stickle et al., 2005; Palmieri, Lavrentieva, & Greenhalgh, 2009; Pannu & Nadim, 2008; Schneider, Khemani, Grushkin, & Bart, 2010; Symons et al., 2007; Vachvanichsanong, Dissaneevate, Lim, & McNeil, 2006) (Table 2.1). Regardless of etiology, the manifestations and clinical consequences of AKI are similar.
Table 2.1: Examples of major causes of acute kidney injury in children

<table>
<thead>
<tr>
<th>Classification</th>
<th>Etiology</th>
</tr>
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<tbody>
<tr>
<td>Pre-renal</td>
<td>Decreased intravascular volume</td>
</tr>
<tr>
<td>Intrinsic</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td></td>
<td>Hypoxia/ischemia</td>
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<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Multiple organ dysfunction syndrome (MODS)</td>
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<tr>
<td></td>
<td>Uric acid nephropathy</td>
</tr>
<tr>
<td></td>
<td>Tumor lysis syndrome</td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>Renal artery/vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Cortical necrosis</td>
</tr>
<tr>
<td></td>
<td>Haemolytic uremic syndrome</td>
</tr>
<tr>
<td>Post-renal</td>
<td>Ureteral or urethral obstruction</td>
</tr>
<tr>
<td></td>
<td>Solitary kidney obstruction</td>
</tr>
</tbody>
</table>

Information from (Andreoli, 2009; Basu et al., 2011)

AKI is traditionally classified by the location of the pathophysiology relative to the kidney; ‘pre-renal’ diseases alter the perfusion of the kidney, affecting oxygen delivery to the organ, ‘intrinsic’ diseases cause damage within the kidneys themselves, and obstructions of the urinary tract are considered ‘post-renal’ injury (Andreoli, 2009; Basu et al., 2011; Zappitelli & Goldstein, 2009). Each of the conditions related to the development of AKI causes renal injury through different mechanisms.

Pre-renal AKI results from renal hypoperfusion, due to low intravascular volume caused by dehydration, fluid shifts outside the intravascular space, or capillary leaks, or low circulating volume from poor cardiac output or systemic vasodilation (Zappitelli & Goldstein, 2009). Pre-renal AKI can also occur due to renal artery stenosis or compression, though this is rare. Regardless of cause, the result is a decrease in the perfusion of the kidney. If renal
hypoperfusion is restored quickly (e.g. a rapid replenishment of fluid volume to the kidney), kidney function may be quickly restored. Otherwise, the process of acute tubular necrosis (ATN) begins. ATN is most commonly caused by a lack of oxygen (ischemia) to renal tissue; other causes of ATN are toxic or vascular insults to the kidney or through inflammatory mechanisms. ATN causes damage to or destruction of the internal structures of the kidneys, particularly the tubules. Once the pathophysiologic processes of ischemic renal injury have been triggered, restoration of intravascular volume will not restore kidney function.

Intrinsic causes of AKI refer to any acute reduction in kidney function as a result of direct damage to renal tissue (Zappitelli & Goldstein, 2009). In the ICU, the most common cause of this form of AKI is acute tubular necrosis (described above). Post-ren al AKI results from obstructions of the urinary tract. In the paediatric ICU setting, this is a rare cause of AKI and is generally related to tumors or ureteral obstructions from mass effect, stones or blood clots. Unappreciated catheter obstructions in children with indwelling Foley catheters may also contribute to the development of post-renal AKI.

2.2.2 Incidence of AKI

The prevalence of AKI in the paediatric hospital setting appears to be increasing (Vachvanichsanong et al., 2006) likely as a result of the increased availability of treatment options for many critical illnesses and advances in paediatric and neonatal critical care (Devarajan, 2013). The incidence of AKI among children admitted to intensive care units has been estimated to range from 10% to 35% (Alkandari et al., 2011; Kavaz et al., 2012; Schneider et al., 2010). In more severely critically ill children, the incidence of AKI has been reported to occur in 90% of patients with traumatic injuries or those needing vasopressor support and requiring mechanical ventilation (Prodhan et al., 2012). The incidence of AKI ranges from 30%
to 50% in children undergoing cardiac surgery (Aydin et al., 2012; Blinder et al., 2012; Fadel et al., 2012; Krawczeski, Woo, et al., 2011; Li et al., 2011; Toth et al., 2012). Even among non-critically ill children receiving nephrotoxic medications, the incidence of AKI has been estimated to be 34% (Moffett & Goldstein, 2011). The wide variability in AKI incidence may be due to differences in the definition of AKI used; however, it is reasonable to postulate that specific populations of critically ill children have higher rates of AKI due to underlying differences in risk.

2.2.3 Outcomes of AKI

AKI has been associated with increased mortality in adult patients. A meta-analysis of 24 studies involving over 71,000 adult patients reported a pooled estimated mortality rate of 31.2% in patients with AKI compared with 6.9% in patients without AKI (Ricci et al., 2008). In children, the short-term outcomes of critically ill children with AKI have been well documented. High mortality rates ranging from 30% to 40% have been consistently reported in critically ill children with AKI (Alkandari et al., 2011; Bresolin et al., 2009; Duzova et al., 2010; Kavaz et al., 2012; Palmieri et al., 2009; Prodhant et al., 2012; Schneider et al., 2010). When compared with other patients, mortality rates are significantly higher among children who develop AKI: in a study of critically ill neonates and children who received extracorporeal membrane oxygenation (ECMO), the adjusted odds of death in patients with AKI was three times higher (95% confidence interval (CI): 2.6-4.0) than in those without AKI (D. J. Askenazi et al., 2009). In addition, a study of 430 infants who had cardiac surgery for congenital defects found that more severe AKI was associated with increased hospital mortality (Blinder et al., 2012). When compared with patients without AKI, the odds of mortality in those who developed AKI ranged from 5.1 (95% CI: 1.7 – 15.2) for patients with moderate AKI to 9.5 (95% CI: 2.9 – 30.7) for
patients with severe AKI. Acute kidney injury is also related to measures of morbidity in children. In a multicentre, retrospective analysis of 2 106 paediatric ICU admissions, AKI was shown to be independently associated with mechanical ventilation and increased ICU stay (Alkandari et al., 2011). Extended use of mechanical ventilation and increased hospital stay have been shown to be independently associated with AKI in children undergoing cardiac surgery (Aydin et al., 2012; Blinder et al., 2012; Li et al., 2011; Toth et al., 2012).

While short-term outcomes of AKI in children have been well documented, little information exists on long-term survival in paediatric patients who develop AKI. Askenazi et al. (2006) followed a cohort of 174 children who developed acute renal failure during their hospitalization and survived to hospital discharge. They found a survival rate of 80% three to five years post-hospital discharge; most deaths (65%) occurred within one year of the initial hospitalization.

It was previously thought that patients who survived an episode of AKI would recover full kidney function; a recent meta-analysis found that adults with AKI were nine times more likely to develop chronic kidney disease and three times more likely to develop end-stage renal disease compared to patients without AKI (Coca, Singanamala, & Parikh, 2012).

In a retrospective study of paediatric inpatients who developed AKI during their hospitalization, two-thirds had recovered full renal function and 15% had improved renal function by hospital discharge, though the definition of ‘recovered’ and ‘improved’ renal function was not clearly stated by the authors (Hui-Stickle et al., 2005). In the same patient cohort, 14% developed chronic renal failure and 5% who were discharged needed ongoing renal replacement therapy (RRT) (Hui-Stickle et al., 2005). Among a cohort of paediatric AKI patients who survived three to five years post-hospital discharge, 29 patients consented to additional renal assessments. Residual renal injury was defined as the presence of any one of: microalbuminuria, hypertension,
hematuria, or an estimated glomerular filtration rate outside a normal range, where normal was
defined as 90-150 ml/min/1.73 m². Fifty-nine percent of patients had signs of renal dysfunction
at the time of follow-up (D. J. Askenazi et al., 2006).

Treatment of AKI in critically ill children focuses on avoiding or minimizing further renal injury
and preventing life-threatening imbalances of fluids or electrolytes (Zappitelli & Goldstein,
2009). Patients with severe AKI or those with severe fluid overload or electrolyte imbalance
may require renal replacement therapy (Kidney Disease: Improving Global Outcomes (KDIGO)
Acute Kidney Injury Working Group, 2012). While modern RRT has largely eliminated the
traditional, life-threatening complications of AKI such as hyperkalemia, arrhythmia, and uremic
coma, children with AKI treated with RRT still have a high mortality rate, ranging from 30% to
50% (Devarajan, 2013; Symons et al., 2007). This high mortality rate has remained stable over
the past two decades (Devarajan, 2013; Symons et al., 2007) and is likely due to a number of
factors. For example, interactions between the kidney and other major organs, known as ‘cross-
talk’, result in cycle of AKI and multi-organ failure, which leads to death (Amann, Wanner, &
Ritz, 2006; Basu & Wheeler, 2013; Grams & Rabb, 2012; Lane, Dixon, Macphee, & Philips,
2013). In addition, AKI also impairs the immune system, increasing a patient’s susceptibility to
infection (Singbartl et al., 2011). AKI also contributes to medication failure: critically ill
children are at substantial risk of ADE (Awdishu & Bouchard, 2011; Eyler & Mueller, 2011;
Perazella, 2012) and under-dosing of medications often occurs due to unstable elimination rates
and volumes of distribution and significant clearance by RRT (Awdishu & Bouchard, 2011;
Eyler & Mueller, 2011; Perazella, 2012). Finally, AKI often results in fluid overload, which has
been shown to be an independent risk factor for mortality in AKI (Sutherland et al., 2010).
2.2.4 Defining AKI

2.2.4.1 Measuring Kidney Function

As the main function of the renal system is the removal of waste products from the body, the glomerular filtration rate (GFR), defined as the volume of plasma cleared of a substance per unit of time, is widely accepted as the most useful overall index of kidney function (Traynor, Mactier, Geddes, & Fox, 2006). Ideally, the best substance to measure GFR is one that is excreted only by the kidneys and not reabsorbed. While inulin meets these criteria, it is not naturally available in the human body. Radioactive markers can also be used to measure GFR (Stevens & Levey, 2009), but these measures are not practical for routine clinical use. Creatinine is the endogenous substance that is closest to an ideal (Chantler, Garnett, Parsons, & Veall, 1969) and creatinine clearance, the amount of creatinine cleared from the blood during a given time period, can be used to estimate GFR. However, measuring creatinine clearance requires a 24 hour urine collection which can be both difficult and inconvenient for patients (Traynor et al., 2006). Creatinine clearance also tends to overestimate the true GFR (Proulx et al., 2005; Toto, 1995).

As such, a number of formulae have been derived to estimate GFR based solely on serum creatinine levels, known as estimated creatinine clearance. In adults, the Modification of Diet in Renal Disease (MDRD) formula is the most widely used ("K/Doqi Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification," 2002). The MDRD estimates GFR using creatinine, age, sex and race (African-American versus other races). The formula is not accurate for use in children, the elderly, those with unusual muscle mass and weight (e.g. morbidly obese patients). In children, the Schwartz formula is widely used (Schwartz, Haycock, Edelmann, & Spitzer, 1976). The Schwartz formula estimates a child’s GFR based on the child’s height and serum creatinine.
In clinical practice, an abrupt decline in GFR, indicative of kidney injury, is assessed by an increase in serum creatinine and/or oliguria. While these measures are limited in their ability to provide early detection of renal injury as changes in serum creatinine may lag behind changes (either decline or recovery) in GFR by several days, changes in serum creatinine and/or urine output are the foundation for diagnostic criteria of AKI (Akcan-Arikan et al., 2007; Bellomo, Ronco, Kellum, Mehta, & Palevsky, 2004; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; R. L. Mehta et al., 2007). Other diagnostic tools, including clinical history, physical examination, renal ultrasound, fractional excretion of sodium (FeNa), fractional excretion of urea, blood urea nitrogen (BUN), and urine microscopy, can provide insight to the etiology of the renal injury.

2.2.4.1.1 Biomarkers

In order to improve the detection of acute kidney injury, a number of new biomarkers have been identified. These markers identify early stress responses of the kidney and appear in the urine or plasma before changes in serum creatinine are evident (Devarajan, 2011). The most widely studied and validated early biomarker of AKI in children is neutrophil gelatinase-associated lipocalin (NGAL). Levels of NGAL in the urine and plasma of children undergoing cardiopulmonary bypass were significantly elevated within 2-6 hours after bypass in children who subsequently developed AKI (Bennett et al., 2008; Dent et al., 2007; Krawczeski, Goldstein, et al., 2011; Krawczeski, Woo, et al., 2011; Mishra et al., 2005; Parikh et al., 2011). Increased NGAL measurements have also been shown to be associated with hospital length of stay and the duration and severity of AKI (Bennett et al., 2008; Dent et al., 2007; Krawczeski, Goldstein, et al., 2011; Krawczeski, Woo, et al., 2011; Parikh et al., 2011). Studies in the paediatric ICU and emergency department settings have shown that increases in NGAL predicted
AKI roughly one to two days before corresponding increases in serum creatinine were evident (Du et al., 2011; Wheeler et al., 2008; Zappitelli et al., 2007). Two recent meta-analyses of NGAL studies in critically ill adults and children have confirmed the clinical utility of this marker as an early indicator of AKI and showed significant associations between increasing NGAL levels and clinical outcomes including mortality, length of stay and the initiation of renal replacement therapy (Haase, Bellomo, Devarajan, Schlattmann, & Haase-Fielitz, 2009; Haase et al., 2011).

Serum cystatin C levels have also been shown to be highly correlated to AKI and can be used as a marker of disease progression after kidney transplantation (Gourishankar, Courtney, Jhangri, Cembrowski, & Pannu, 2008). In addition, kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and liver fatty acid binding-protein have been shown to be associated with renal ischemia (Devarajan, 2008; Parikh, Edelstein, Devarajan, & Cantley, 2007). However, recent studies have reported relatively low predictive abilities of biomarkers to predict worsening kidney function; when combined with clinical markers, their predictive ability increases (Arthur et al., 2014; Hall et al., 2011; Koyner et al., 2012; Koyner et al., 2010). For example, in a study of patients with AKIN-defined stage 1 kidney injury after cardiac surgery, IL-18 best predicted the worsening of AKI or death compared with the other 32 biomarkers assessed, with an area under the curve (AUC) of 0.74 (Arthur et al., 2014). However, this level of accuracy is moderate (Fischer, Bachmann, & Jaeschke, 2003). The predictive ability of IL-18 increased when it was combined with the percent change in serum creatinine (Arthur et al., 2014). The use of biomarkers is a rapidly evolving field; however, to date, biomarkers have not been incorporated into clinical practice and thus are not currently a practical method to assess and diagnose acute kidney injury.
2.2.4.2 Current Definitions of AKI

More than 35 definitions of AKI have been used in the literature (R. L. Mehta & Chertow, 2003). In order to promote a consistent definition of AKI to allow for comparison of study results, the Acute Dialysis Quality Initiative convened an international consensus panel in 2002 and proposed the RIFLE criteria for use in critically ill adults (Bellomo et al., 2004). Based on changes from the patient’s normal (baseline) kidney function, the RIFLE classifies increasing severity of acute kidney injury into 5 categories: Risk (R), Injury (I), Failure (F), Loss of kidney function (L), and End-stage kidney disease (E) (Table 2.2). The first three severity levels (Risk, Injury and Failure) are assessed by changes in glomerular filtration rate from a baseline measure and urine output. The worst of these measures define a patient’s severity level. For example, consider a patient whose creatinine has increased 1.5 times from their baseline measure and whose urine output is 0.4 ml/kg/h x 12h. According to the GFR criteria, the patient’s AKI severity meets the ‘Risk’ definition, but their urine output meets the ‘Injury’ criteria. As such, the patient would be classified according to their urine output and be diagnosed as having an AKI severity of ‘Injury’. The length of renal replacement therapy (RRT) defines the final two severity levels (Loss and End-stage). When a measure of the patient’s baseline GFR is not available or is unknown, the panel suggested assuming a GFR of 75ml/min/1.73m², the lower limit of normal (Bellomo et al., 2004).

A modification of the RIFLE (known as the pRIFLE) has been suggested for use in paediatric populations (Akcan-Arikan et al., 2007). The changes are minor and include a focus on the estimated creatinine clearance, calculated using the Schwartz formula (Schwartz, Haycock, Edelmann, et al., 1976), as the measure of GFR. In addition, the threshold for the ‘Failure’ category was modified from a serum creatinine ≥ 4 mg/100ml to an estimated creatinine
clearance (eCCL) < 35 ml/min/1.73m², and the time interval for the urine output criteria was increased from 6 hours to 8 hours (Table 2.2).

In 2005, the Acute Kidney Injury Network (AKIN) reviewed and modified the RIFLE criteria, recognizing that even very small changes in serum creatinine are associated with adverse clinical outcomes (Coca, Peixoto, Garg, Krumholz, & Parikh, 2007; Eric A. J. Hoste et al., 2006; Lassnigg et al., 2004; Nash, Hafeez, & Hou, 2002; Ostermann & Chang, 2007; Shigehiko Uchino et al., 2006). According to the AKIN, AKI is defined as “an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥26.4 µmol/L), a percentage increase in serum creatinine of ≥50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of <0.5 mL/kg/hr for >6 hrs)” (R. L. Mehta et al., 2007) (Table 2.2). Similar to the RIFLE, the AKIN definition also defines levels of severity, defined as Stages 1, 2 and 3, which correspond to RIFLE severity levels of ‘Risk’, ‘Injury’ and ‘Failure’, respectively. Also similar to the RIFLE, the AKIN is based on both changes in creatinine and urine output; however, it also adds a measure of time. The time constraint of 48 hours for diagnosis was selected based on evidence that small increases in creatinine within 24 to 48 hours were associated with a threefold increase in 30-day mortality (Lassnigg et al., 2004). Studies have shown that the RIFLE and AKIN criteria show concordance in critically ill patients (Bagshaw, George, Bellomo, & Committe, 2008; Lopes et al., 2008). However, evidence has shown that the RIFLE captures more mild cases of acute kidney injury than the AKIN (Zappitelli, Moffett, Hyder, & Goldstein, 2011) and the AKIN classification does not improve outcome prediction over the RIFLE (Bagshaw et al., 2008; Chang et al., 2010).
Recognizing the need for a single consensus definition and staging system that could be applied to both children and adults, the Kidney Disease: Improving Global Outcomes (KDIGO) group proposed a new definition of AKI in 2012 that incorporates the RIFLE, pRIFLE and AKIN classifications (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) (Table 2.2). Both the binary definition of AKI and the severity scale feature a 0.3 mg/dl increase in serum creatinine to specifically be applicable to paediatric AKI. The KDIGO staging also allows for a child with an estimated GFR <35 mL/min per 1.73m$^2$ to be classified as high severity (Stage 3), in contrast with the adult criterion of $\geq$4 mg/dl which would be unrealistic in infants and young children.
Table 2.2: Current criteria used for the diagnosis of acute kidney injury

<table>
<thead>
<tr>
<th>Classification</th>
<th>Stage</th>
<th>Creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIFLE (Bellomo et al., 2004)</td>
<td>Risk</td>
<td>Increased creatinine x1.5 or GFR decrease &gt;25%</td>
<td>&lt;0.5 ml/kg/h x 6h</td>
</tr>
<tr>
<td></td>
<td>Injury</td>
<td>Increased creatinine x2 or GFR decrease &gt;50%</td>
<td>&lt;0.5 ml/kg/h x 12h</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>Increased creatinine x3 or GFR decrease &gt;75% or creatinine ≥4 mg/100ml (acute rise of ≥0.5 mg/100ml dl)</td>
<td>&lt;0.3 ml/kg/h x 24h or anuria x 12h</td>
</tr>
<tr>
<td></td>
<td>Loss</td>
<td>Persistent ARF = complete loss of renal function &gt; 4 weeks (defined as the need for renal replacement therapy (RRT) for &gt;4 weeks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End-stage</td>
<td>End-stage renal disease (defined as the need for dialysis for &gt;3 months)</td>
<td></td>
</tr>
<tr>
<td>Pediatric RIFLE (pRIFLE) (Akcan-Arikan et al., 2007)</td>
<td>Risk</td>
<td>eCCl decrease by 25%</td>
<td>&lt;0.5 ml/kg/h x 8h</td>
</tr>
<tr>
<td></td>
<td>Injury</td>
<td>eCCl decrease by 50%</td>
<td>&lt;0.5 ml/kg/h x 16h</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>eCCl decrease by 75% or eCCl &lt;35 ml/min/1.73m²</td>
<td>&lt;0.3 ml/kg/h x 24h or anuria x 12h</td>
</tr>
<tr>
<td></td>
<td>Loss</td>
<td>Persistent failure &gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End-stage</td>
<td>End-stage renal disease (persistent failure &gt;3 months)</td>
<td></td>
</tr>
<tr>
<td>AKIN (R. L. Mehta et al., 2007)</td>
<td>1</td>
<td>Increased creatinine x 1.5-2 or creatinine increase ≥0.3 mg/dl</td>
<td>&lt;0.5 ml/kg/h x 6h</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increased creatinine x 2-3</td>
<td>&lt;0.5 ml/kg/h x 12h</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increased creatinine x ≥3 or creatinine ≥4.0 mg/dl with an acute increase of 0.5 mg/dl</td>
<td>&lt;0.3 ml/kg/h x 24h or anuria x 12h</td>
</tr>
<tr>
<td>KDIGO (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012)</td>
<td>1</td>
<td>Increased creatinine x1.5-1.9 or ≥0.3 mg/dl increase</td>
<td>&lt;0.5 ml/kg/h x 6-12h</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increased creatinine x2.0-2.9</td>
<td>&lt;0.5 ml/kg/h x ≥12h</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increased creatinine x3 or creatinine ≥4.0 mg/dl or initiation of RRT or eGFR &lt;35 ml/min per 1.73m² (&lt;18 years)</td>
<td>&lt;0.3 ml/kg/h x ≥24h or anuria x ≥12h</td>
</tr>
</tbody>
</table>

AKIN: Acute Kidney Injury Network; GFR: glomerular filtration rate; eCCl: estimated creatinine clearance; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; RRT: renal replacement therapy
Little evidence exists in the literature regarding the benefit of the KDIGO criteria over other consensus definitions. Some studies have shown differences between the RIFLE or AKIN and the new KDIGO definition. For example, a study of various AKI definitions in adult patients admitted with heart failure reported an AKI incidence of 36.7% based on KDIGO compared to incidence rates of 25.6% and 27.9% according to the RIFLE and AKIN, respectively (Roy et al., 2013). Despite the differences in estimated incidence, there were no differences between the three definitions in terms of their predictive ability of 30-day and one-year adverse events, defined as a composite of heart failure-related hospital admission, renal replacement therapy, and all-cause mortality. Another study of adult patients with acute myocardial infarction (AMI) found the incidence of AKI during the first 7 days of hospitalization to be 14.8% and 36.6% according to the RIFLE and KDIGO definitions, respectively (Rodrigues et al., 2013). Patients diagnosed as having AKI by the KDIGO definition but not by RIFLE had significantly higher 30-day and one-year mortality. Other studies have shown no significant difference between the definitions: patients undergoing cardiac surgery had post-surgical AKI rates of 25.9% according to either the AKIN or KDIGO and 24.9% based on the RIFLE (Bastin et al., 2013). All studies were performed in adult patient populations and used only the serum creatinine criteria of the definitions, ignoring any effect of urine output on the estimated incidence of AKI. A recent study compared the pRIFLE, AKIN and KDIGO definitions in children. Lex et al applied the 3 different definitions in a cohort of 1489 consecutive paediatric patients who underwent cardiac surgery and found differences in the estimated incidence of AKI (Lex et al., 2014). According to the AKIN criteria, 20% of patients had AKI. The estimated incidence increased to 29% and 34% according to the KDIGO and pRIFLE definitions, respectively. As in adult studies, the presence and severity of AKI was assessed for each classification using only changes in serum creatinine.
or estimated creatinine clearance; the urine output component of the definitions was not considered.

Finally, similar to the idea of cardiac angina, the concept of ‘renal angina’ has recently been introduced to identify patients who may benefit the most from early treatment to manage or prevent the development of AKI (Basu, Chawla, Wheeler, & Goldstein, 2012; S. L. Goldstein & Chawla, 2010). There are few signs and symptoms in the early stages of AKI when interventions are likely to be the most effective and the definition places children at moderate, high or very high risk of developing AKI. As the risk for AKI increases, less laboratory evidence of AKI (i.e. specified changes of serum creatinine) is needed to meet the threshold for a diagnosis of renal angina. In order to be classified as having a moderate risk of AKI, patients need to be admitted to the ICU and experience either a two-fold increase in serum creatinine or a fluid overload of more than 15%. Stem cell transplant patients or those with heart failure who have a serum creatinine increase of at least 0.3 mg/dl or a fluid overload of more than 10% are classified as high risk, whereas patients with mechanical ventilation and any increase in serum creatinine or a fluid overload of more than 5% are considered to be at very high risk for AKI.

Recently, the idea of renal angina has been further developed into an index for use in critically ill children (Basu et al., 2013). To calculate the renal angina index, a patient is assigned a score based on their risk of AKI (hereafter referred to as the risk of AKI score); patients who are admitted to the ICU are deemed to be at ‘moderate’ risk and given a score of 1. Patients who have undergone stem cell transplantation are at ‘high’ risk and given a score of 3; patients who are ventilated and prescribed inotropes are deemed to be at ‘very high’ risk, which equates to a score of 5. Similar scores are given to patients based on the signs of renal injury, assessed by changes in estimated creatinine clearance (eCCl) and fluid overload. Based on the combination
of eCCI and FO, patients are given scores of 1 (no change in eCCI, fluid overload <5%), 2 (eCCI decrease between 0-25%, fluid overload ≥5%), 4 (eCCI decrease of 25-50%, fluid overload ≥10%) or 8 (eCCI decrease ≥50%, fluid overload ≥15%). The renal angina index is calculated by multiplying the risk of AKI score and the signs of injury score, resulting in a value between 1 and 40. The renal angina index was validated in three cohorts of critically ill patients by comparing its predictive performance against the KDIGO definition of AKI and illness severity scores (Basu et al., 2013).

For the purposes of this thesis, the RIFLE definition of AKI was utilized. Both the KDIGO definition and the renal angina index were published after the majority of the thesis work was completed. The RIFLE definition was chosen over the AKIN because, as previously stated, the RIFLE has been shown to capture more mild cases of acute kidney injury than the AKIN (Zappitelli et al., 2011) and the AKIN classification does not improve outcome prediction over the RIFLE (Bagshaw et al., 2008; Chang et al., 2010). Finally, the proposed modification to the RIFLE for use in paediatric populations (known as the pRIFLE (Akcan-Arikan et al., 2007)) provides limited justification for the changes made to the original RIFLE (Akcan-Arikan et al., 2007). Modification of the urine output assessment from a 6 hour to an 8 hour interval may be illustrative of pragmatic customization of the RIFLE due to institutional practice or difficulties with measurement accuracy. Accordingly, AKI was defined as per the RIFLE definition for this dissertation.
2.3 Adverse Drug Events

Pharmacotherapy plays an integral role in health care. Medications are used to treat primary disease, to facilitate the initiation and continued use of mechanical organ support, such as mechanical ventilation, as well as to counteract effects of other medications. However, medications may also have unwanted side effects that can range from easily recognized physical symptoms (i.e. rashes) to other reactions that may be difficult to associate with a specific drug (i.e. confusion or organ dysfunction). In a sample of 30 195 randomly selected hospital records, the Harvard Medical Practice Study identified 1 133 patients (3.7%) with injuries caused by medical treatment (Leape et al., 1991). Adverse events have high rates of mortality and morbidity: while not all morbidity and mortality may be directly attributable to an adverse event, up to 30% of adult patients with complications die or experience disability more than 6 months after the adverse event (Brennan et al., 1991). The study found that the most common adverse events experienced by hospitalized patients were complications from medications, accounting for over 19% of detected events (Leape et al., 1991). Using similar methodology as the Harvard Medical Practice Study, the Canadian Adverse Events Study reported a rate of 7.5 adverse events per 100 hospital admissions (Baker et al., 2004). The authors reported the most common types of adverse events were related to surgical procedures (34.2% of detected events), followed by drug- or fluid-related events (23.6%). A recent Canadian study focused on estimating the incidence of adverse events in paediatric patients (Matlow et al., 2012). The authors reviewed 3 669 admissions to 8 academic paediatric hospitals and 14 community hospitals across Canada and reported a incidence rate of 9.2%, weighted for the sampling strategy. Adverse events were most commonly related to surgery (32.9%); however, drugs (13.5%), anaesthesia (2.5%) and fluids (0.8%) were also attributed to the occurrence of an adverse event in paediatric patients.
Unintended drug reactions can be defined in a number of ways. An adverse drug reaction (ADR) is considered to be an unintended and noxious response that occurs under normal or expected uses of a drug ("International Drug Monitoring. The Role of the Hospital," 1969). Adverse drug reactions rank as the fifth leading cause of death and illness in the developed world, estimated to claim between 100,000 and 218,000 lives annually (Ernst & Grizzle, 2001; White, Arakelian, & Rho, 1999). However, ADRs consider only episodes in which the use of the drug is appropriate, whereas many adverse events can be attributed to other factors including, but not limited to, error (Bates, Leape, & Petrycki, 1993). As such, an adverse drug event (ADE) is defined as any injury or harm related to the use of a drug ("Ashp Guidelines on Preventing Medication Errors in Hospitals," 1993). As such, adverse drug reactions are considered a subset of adverse drug reactions (Figure 2.2); the definition of an ADE includes non-preventable occurrences, such as unpredictable drug rashes and expected events such as complications of chemotherapy, as well as preventable incidents caused by errors in prescribing, dispensing or administering drugs. This broader definition of drug-associated harm will be used in this thesis.
Figure 2.2: Representation of the relationship between adverse drug reactions, adverse drug events and the intersection between error and harm

Adapted from the Bates model of medication errors, potential adverse drug events and adverse drug events (Bates, Boyle, Vander Vliet, Schneider, & Leape, 1995). All errors do not result in an adverse drug event, nor are all adverse drug events a result of error. ADEs that are a result of error are known as preventable ADEs. Adverse drug reactions (ADRs) are a subset of ADEs as they consider only events that occur after appropriate drug therapy.

ADE: adverse drug event; ADR: adverse drug reaction

It should be noted that while adverse drug events encompass injury caused by error, not all ADEs are caused by error, nor do all errors result in harm (Bates, Boyle, et al., 1995). Several studies have suggested that roughly one-third of ADEs are associated with medication errors and thus are considered to be preventable events (Bates, Cullen, et al., 1995; Bates et al., 1993). The medication process is comprised of 5 stages: prescription, transcription, preparation, dispensing
and administration (Hussain & Kao, 2005); errors can occur at any step in this process. Most errors occur in the administration stage (53% of all errors), followed by prescription (17%), preparation (14%) and transcription (11%) (Krahenbuhl-Melcher et al., 2007). While only 10% of medication errors result in an ADE, these errors have implications for patients and health care providers (Barker, Flynn, Pepper, Bates, & Mikeal, 2002; Bates, Boyle, et al., 1995; Calabrese et al., 2001).

Adverse drug events are common in hospitalized patients, occurring at rates of 6.5 per 100 adult admissions, and result in significantly higher hospital stays and resource utilization (Bates, Cullen, et al., 1995; Bates et al., 1997; Cullen et al., 1997; Lazarou, Pomeranz, & Corey, 1998).

2.3.1 At Risk Populations: Critical Illness and Children

Adverse drug events are common in the intensive care unit (ICU). Providing a critically ill patient with a single dose of a single medication requires the health care provider to correctly execute anywhere from 80 to 200 steps (Hussain & Kao, 2005). During a one-year, prospective observational study of adult patients, the Critical Care Safety Study found that almost half (47%) of adverse events observed in the medical intensive care and coronary care units of an academic hospital were drug-related (Rothschild et al., 2005). Among errors deemed as ‘serious’, defined as those that caused harm or injury or had the potential to cause harm, medications were responsible for 78% (Rothschild et al., 2005). Given that patients in the ICU have substantially higher morbidity and mortality than other hospital inpatients, it is unsurprising that the rates of ADEs in the ICU are higher than those for other hospitalized patients (Bates, Cullen, et al., 1995; Cullen et al., 1997). The severity of adverse events is also higher in critically ill patients; a prospective cohort study of all adult admissions to medical and surgical intensive care units and
general care units found that 26% of ADEs occurring in ICUs were classified as life threatening compared to 11% in non-ICU patients (Cullen et al., 1997).

The ICU environment is complex and brings together high-risk patients and interventions with a narrow therapeutic index. Critically ill patients are vulnerable to ADEs due to their illness severity (Valentin et al., 2006), the intensity of their treatment, including complex drug regimens (Pronovost et al., 2003; Rothschild et al., 2005), sedation and mechanical ventilation (Beckmann et al., 2003; Hussain & Kao, 2005), as well as altered organ function which can affect the pharmacokinetics of drugs (Table 2.3). Critically ill patients are prescribed twice as many medications as other inpatients (Cullen et al., 1997) and usually receive multiple drugs and complex drug combinations. The risk of an ADE increases with each additional drug used (Impicciatore et al., 2001; Silva et al., 2013), likely due to drug interactions (May, Stewart, & Cluff, 1977; Rothschild et al., 2005). Thus, it is far more likely that adverse events will occur in the intensive care setting compared to other inpatient areas of the hospital.

A wide variety of drugs have been associated with adverse drug events, with no group or class of drugs reported to cause a disproportionate share of ADEs (Bates, Cullen, et al., 1995; Cullen et al., 1997). In addition, environmental characteristics of ICUs may lead to higher rates of ADEs and medication errors, including the fast pace of care, frequent personnel changes and handoffs of care, communication challenges, loud noise, and frequent work interruptions (Camire, Moyen, & Stelfox, 2009; Donchin et al., 1995; Donchin & Seagull, 2002; Kane-Gill & Weber, 2006).
Table 2.3: Risk factors of adverse drug events in the intensive care unit

<table>
<thead>
<tr>
<th>Factors</th>
<th>Specific risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Illness severity</td>
</tr>
<tr>
<td></td>
<td>Strongest predictor of ADE</td>
</tr>
<tr>
<td></td>
<td>ICU patients more likely to experience ADE than other hospitalized patients</td>
</tr>
<tr>
<td></td>
<td>Extreme ages</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility to ADEs</td>
</tr>
<tr>
<td></td>
<td>Prolonged hospitalization</td>
</tr>
<tr>
<td></td>
<td>Increased exposure and susceptibility to ADEs</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Patients unable to participate in care</td>
</tr>
<tr>
<td>Medications</td>
<td>Types of medications</td>
</tr>
<tr>
<td></td>
<td>Frequent use of boluses and infusions</td>
</tr>
<tr>
<td></td>
<td>Weight-based infusions derived from estimated weights or unreliable determinations</td>
</tr>
<tr>
<td></td>
<td>Mathematical calculations required for medication dosages</td>
</tr>
<tr>
<td></td>
<td>Programming of infusion pumps</td>
</tr>
<tr>
<td></td>
<td>Number of medications</td>
</tr>
<tr>
<td></td>
<td>Twice as many medications prescribed as for other hospitalized patients</td>
</tr>
<tr>
<td></td>
<td>Increased probability of medication error and medication interactions</td>
</tr>
<tr>
<td></td>
<td>Number of interventions</td>
</tr>
<tr>
<td></td>
<td>Increased risk of complications</td>
</tr>
<tr>
<td>ICU environment</td>
<td>Complex environment</td>
</tr>
<tr>
<td></td>
<td>Difficult working conditions make errors more probable</td>
</tr>
<tr>
<td></td>
<td>High stress</td>
</tr>
<tr>
<td></td>
<td>High turnover of patients and providers</td>
</tr>
<tr>
<td></td>
<td>Emergency admissions</td>
</tr>
<tr>
<td></td>
<td>Risk of an adverse event increases by approximately 6% per day</td>
</tr>
<tr>
<td></td>
<td>Multiple care providers</td>
</tr>
<tr>
<td></td>
<td>Challenges the integration of different care plans</td>
</tr>
</tbody>
</table>

Information from (Camire et al., 2009; Moyen, Camire, & Stelfox, 2008)
ADE: adverse drug event; ICU: intensive care unit

Paediatric patients may be at an additional increased risk of experiencing harm from a medication. A systematic review of studies reporting adverse drug reactions in children found the incidence of adverse drug events in children was estimated to range from 4.3 to 16.7% (Impicciatore et al., 2001). The authors reported the pooled average incidence of ADEs, adjusted
and weighted according to study sample size, as 9.5% (95% CI: 6.8-12.3). Hospitalized children may be at higher risk of an adverse event (Gill et al., 1995); 14 to 17% of paediatric hospitalizations result in adverse drug reactions with roughly 28% of these reactions being severe, resulting in high rates of morbidity and mortality (Gonzalez-Martin, Caroca, & Paris, 1998; Impicciatore et al., 2001; Martinez-Mir et al., 1999; Smyth et al., 2012). The number of potential adverse drug events has been shown to be higher in paediatric inpatients than in adult inpatients (Kaushal et al., 2001). Amongst paediatric inpatients, the greatest numbers of adverse drug events occur in critical care units (Kilbridge et al., 2009; Le, Nguyen, Law, & Hodding, 2006).

Paediatric patients have an increased risk of adverse drug events for a number of reasons. First, there are important pharmacokinetic differences during childhood and early adolescence due to changes in body composition and organ function (Anderson, 2002; Fernandez et al., 2011; Niederhauser, 1997). In addition, children also pose unique challenges during the ordering, dispensing, administering and monitoring of medications. For example, as weight-based dosing is required for most medications in paediatrics, ordering drugs typically involves more calculations compared to dosing in adult patients. Dispensing drugs is also prone to error as pharmacists must often dilute stock solutions for use in children (Koren & Haslam, 1994). A systematic review of medication errors in paediatric patients found that the most common type of error was a dosing error, many of which involve an incorrect dosage of 10 times more or less than the required dose, known as a ten-fold error (Ghaleb et al., 2006).

### 2.3.2 Common Adverse Drug Events in Paediatric Populations

In 2012, a systematic review of observational studies of adverse drug reactions in children was conducted. The authors reviewed studies of ADRs causing admission to hospital, occurring
during hospital stay and occurring in the community setting (Smyth et al., 2012). The authors reported that incidence rates for adverse drug reactions causing hospital admission ranged from 0.4% to 10.3% of all children. For children exposed to a drug during their hospitalization, the incidence of adverse drug reactions ranged from 0.6% to 16.8% (Smyth et al., 2012).

To date, the largest prospective evaluation of ADEs in pediatric inpatients was a cohort study of 1,120 children admitted to 2 academic hospitals over a six-week period (Kaushal et al., 2001). The authors evaluated 10,778 drug orders and found 26 ADEs. However, they did not report disaggregated results according to the type of ADE, the number of drug administrations (compared to the number of drug orders) or the proportion of critically ill patients. One study of 357 written medication orders and 236 drug administration observations occurring within 26 12-hour periods in a pediatric ICU (PICU) found 3 ADEs per 100 orders (Buckley, Erstad, Kopp, Theodorou, & Priestley, 2007). A 2013 prospective cohort study of critically ill pediatric patients reported an incidence rate of 35.1%, with 110 ADEs occurring in 84 patients (Silva et al., 2013).

There is limited literature on specific adverse drug events in pediatric populations as ADEs are generally reported in aggregate form. Kaushal et al. found that hypokalemia (41.3% of all ADEs), hypomagnesemia (11.9%) and nephrotoxicity (11.3%) were the most commonly found ADEs in a prospective cohort of hospitalized children (Kaushal et al., 2001). A recent study of adverse drug events in a pediatric intensive care unit reported that hyponatremia, hyperglycemia, hypokalemia, and skin rashes were the most commonly observed ADEs (Silva et al., 2013). However, most studies report the incidence of a specific list of adverse events defined a priori; thus, studies will only capture the adverse events that were pre-specified and thus may not capture all possible events associated with a specific drug.
While specific adverse events are not widely reported, a wide variety of drugs have been associated with adverse drug events. A recent systematic review of observational studies reported that anti-infectives, anti-epileptics, non-steroidal anti-inflammatories (NSAIDs) and corticosteroids were the most frequent drug categories associated with adverse drug reactions (Smyth et al., 2012). A prospective cohort study of 1,120 paediatric patients reported that antibiotics, analgesics and sedatives were the most common drug categories involved in errors and potential ADEs, followed by electrolytes and fluids (Kaushal et al., 2001). Reactions involving antibiotics were usually mild whereas anticonvulsants and antineoplastic agents were associated with more severe reactions. Other studies of adverse drug events in paediatric populations have shown slightly differing results. A review of voluntary safety reports and computerized surveillance of medication-related events at a paediatric hospital found that nephrotoxins, narcotics and benzodiazepines and hypoglycaemia were the most frequent categories of adverse drug events captured by these surveillance systems (Ferranti, Horvath, Cozart, Whitehurst, & Eckstrand, 2008). An automated surveillance system developed to identify adverse drug events in a paediatric hospital found hypokalemia, hypomagnesemia, nephrotoxicity and opiate overdose identified through naloxone administration among the most common ADEs detected during the 6-month study period (Kilbridge et al., 2009). The authors also found that diuretics, antibiotics, immunosuppressants, narcotics and anticonvulsants were the most common medications implicated in an ADE. These results are similar to those of Silva et al (2013) who conducted a prospective chart review of consecutive admissions to the paediatric ICU over a 6-month period and reported that antibiotics, diuretics, anti-epileptics, sedatives and analgesics, and steroids were the most common classes of drugs associated with adverse drug events.
2.3.3 Importance of Understanding and Identifying the Contribution of Medications to Adverse Events

While there is extensive literature on drug safety and adverse drug events in adults, little is known about medication safety in paediatric populations, despite their apparent increased risk. Safety data describing adverse drug events in paediatric populations are not well described (Gilman & Gal, 1992; Uppal, Dupuis, & Parshuram). More than 75% of pharmaceuticals licensed in North America have never been tested in paediatric populations and are used without adequate guidelines for safety or efficacy (Leeder, 2003; Uppal et al., 2008). Regardless, use of medications without paediatric indication is common and almost considered to be standard practice (Bavdekar & Gogtay, 2005; Blumer, 1999; Choonara & Conroy, 2002; Conroy & McIntyre, 2005; Cuzzolin, Zaccaron, & Fanos, 2003; Dick et al., 2003; Kimland, Bergman, Lindemalm, & Bottiger, 2007; Pandolfini, Campi, Clavenna, Cazzato, & Bonati, 2005; Pandolfini et al., 2002). Off-label use of medications in paediatric medicine is reported to account for approximately 50-75% of medication use in children (Roberts, Rodriguez, Murphy, & Crescenzi, 2003). A recent retrospective review of administrative clinical data from a neonatal intensive care unit (NICU) found that the United States Food and Drug Administration approved only 35% of the medications routinely used in the NICU for use in infants (Hsieh et al., 2013). Recommended doses of drugs used in children are often based on extrapolations from adult doses using weight, body surface area and age and often ignore pharmacokinetic and pharmacodynamics properties of the drug, increasing susceptibility to drug-related adverse events (Hussain & Kao, 2005; Kaushal et al., 2001; Niederhauser, 1997).

A lack of safety information for children has resulted in the use of a number of therapies and medications with deleterious effects. For example, oxygen therapy to improve breathing for
neonates in incubators was a widely accepted treatment in the 1930s (Zito et al., 2008). In the 1940s, increases in dosage and exposure length were routine practice despite a lack of evidence supporting this practice. This resulted in a substantial increase in the incidence of retrolental fibroplasia, now known as retinopathy of prematurity (ROP) (Kinsey & Zacharias, 1949). Considerable debate followed, which suggested that prematurity was responsible for the disease; finally in 1952, a study definitively linked increase oxygen with the development of retinopathy of prematurity and blindness in premature babies (Patz, 1957).

Pemoline, used for the treatment of attention-deficit/hyperactivity disorder (ADHD), is another example that clearly illustrates the challenges of drug safety for children. Early evidence of hepatotoxicity was evident in adults; however, the relatively low use in children translated into usage of the drug for over 21 years before it was associated with liver toxicity and fatalities in children (Safer, Zito, & Gardner, 2001). Though warnings were added along with requirements for biweekly liver enzyme monitoring, evidence suggested that prescribers were not compliant with the safety directives (Willy, Manda, Shatin, Drinkard, & Graham, 2002). The drug was voluntarily withdrawn in 2005; Health Canada withdrew approval in 1999 and the United States Food and Drug Administration (FDA) withdrew approval in 2005 (Etwel, Rieder, Bend, & Koren, 2008).

Extrapolating drug safety data from adult populations to paediatric populations is not recommended. Key differences between adult and paediatric use include dose, frequency of administration, route of administration and indication for use (Hussain & Kao, 2005), resulting in different effects in children and adults. For example, milrinone increases mortality in adult patients with heart failure, but is both safe and effective in children (Hoffman et al., 2002; Packer et al., 1991). Numerous examples suggest that while adult safety data may drive drug
availability for children, treatment in paediatric populations differs and requires appropriate safety and effectiveness evaluations. Even within paediatric populations clinically important pharmacologic differences exist (Hussain & Kao, 2005; Kearns, 2000; Kearns et al., 2003).

Adding to this problem is the challenge that clinicians face in understanding the relative contribution of drugs versus disease processes to suspected adverse events (Carleton et al., 2009). Determining the occurrence of adverse events is a complex task as the symptoms of the event may overlap with the patient’s underlying disease or may be caused by several unrelated factors including unknown drug allergies of the patient or human error. Drug-related factors such as toxicity, time of administration, dosage and duration of use can also impact the probability of an ADE. In general, if ADEs are not specifically looked for, it is unlikely that they will be identified (Kelly, 2008).

2.3.4 Drug Toxicity as a Cause of AKI

As a major function of the kidney is the excretion of metabolites and drugs, it is unsurprising that the kidney is vulnerable to toxicity.

2.3.4.1 Factors Associated with Increased Toxicity

A number of factors increase the risk of nephrotoxic kidney injury; these factors can be thought of as being patient-specific, kidney-specific or drug-specific (Perazella, 2009).

2.3.4.1.1 Patient-Specific Factors

Patients may be predisposed to develop kidney injury due to a number of factors such as age, gender, body composition and underlying comorbid conditions. The genetic makeup of a patient may also increase their vulnerability to nephrotoxins (Ciarimboli et al., 2005; Harty, Johnson, &
Power, 2006; Ulrich, Bigler, & Potter, 2006). Known as the study of pharmacogenetics, these genetic differences between patients may explain the variations of responses to medications across patients. The cytochrome P450 (CYP450) enzyme system has been well studied in relation to hepatotoxicity. Several polymorphisms are associated with reduced metabolism and subsequent end-organ toxicity. CYP450 enzymes are also found in the kidney; it is reasonable to expect that certain gene expressions that reduce metabolism would increase nephrotoxic risk (Perazella, 2009).

2.3.4.1.2 Kidney-Specific Factors

Kidney-specific factors, such as the high rate of blood delivery (approximately 20-25% of cardiac output) and the high metabolic rate of tubular cells, promote increased sensitivity to injury when the kidneys are exposed to a nephrotoxic substance (Cummings & Schnellmann, 2001; Perazella, 2009).

2.3.4.1.3 Drug-Specific Factors

Factors specific to the drug also play an important role in the development of renal injury. Factors including urine pH, renal excretion of toxic metabolites and rapid parenteral or high dosing (resulting in high peak serum and urine concentrations) enhance the risk of precipitation and crystal formation in the tubules (Guo & Nzerue, 2002; Singh, Ganguli, & Prakash, 2003).

Concurrent drug administration may increase the risk of nephrotoxicity. For example, combinations such as aminoglycosides and cephalothin or cisplatin and non-steroidal anti-inflammatory drugs (NSAIDs) and radiologic contrast are examples of situations with increased nephrotoxic risk to the patient (Evenepoel, 2004; Guo & Nzerue, 2002; Singh et al., 2003; Wyatt, Arons, Klotman, & Klotman, 2006). Even with brief or low levels of exposure, some drugs,
such as aminoglycosides, amphotericin B, adefovir and cidofovir, are highly nephrotoxic and promote renal injury (Alexander & Wingard, 2005; Gambaro & Perazella, 2003; Izzedine, Launay-Vacher, & Deray, 2005; Perazella, 2005; Rougier et al., 2003; Schetz, Dasta, Goldstein, & Golper, 2005).

Drugs can cause renal injury through several mechanisms (Table 2.4) (Pannu & Nadim, 2008; Patzer, 2008; Perazella, 2012; Schetz et al., 2005). Most commonly, drugs that are excreted through the renal system can directly damage renal tubules, causing cellular injury and death (acute interstitial nephritis). Other types of nephrotoxic injury include osmotic nephrosis caused by hypertonic solutions or tubular obstruction caused by drug precipitation (i.e. crystalline nephropathy). While the specific mechanisms of cellular injury caused by these medications are beyond the scope of this thesis work, a few examples are provided. For example, the use of aminoglycosides can result in the accumulation of high concentrations of the drug in lysosomes within the kidney. Once released into the cells, this interrupts the phospholipid cell membrane and promotes oxidative stress and mitochondrial injury and results in proximal tubular cell death, leading to acute kidney injury (Perazella, 2009). Amphotericin B disrupts the cellular membranes, increasing their permeability, resulting in tubular dysfunction (Alexander & Wingard, 2005). The metabolism of cidofovir produces a specific metabolite which interferes with the synthesis and degradation of phospholipids within the cell membrane, resulting in tubular injury (Izzedine et al., 2005; Perazella, 2005).
Table 2.4: Common drugs known to have nephrotoxic effects, categorized by mechanism of injury

<table>
<thead>
<tr>
<th>Mechanism of injury</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-renal failure</td>
<td>ACE inhibitors, cyclosporine A, norepinephrine, NSAIDs, tacrolimus</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>acetaminophen, Antibiotics: aminoglycosides, cephalosporins, amphotericin B, vancomycin, fosfarnet, cisplatinum, contrast media, cyclosporine A, dextran, immunoglobulin, mannitol, NSAIDs</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>acetylsalicylic acid (ASA), allopurinol, Antibiotics: ciprofloxacin, methicillin, penicillin, ampicillin, cephalosporins, oxacillin, rifampicin, contrast media, furosemide, NSAIDs, phenytoin</td>
</tr>
<tr>
<td>Tubular obstruction</td>
<td>acyclovir, methotrexate, methoxyflurane, protease inhibitors, sulfonamides</td>
</tr>
</tbody>
</table>

Information from (Arany et al., 2008)
ACE: angiotensin-converting-enzyme; NSAID: non-steroidal anti-inflammatory
Prolonged therapy at high doses may exacerbate any of the mechanisms described above based solely on increased exposure (Perazella, 2009).

### 2.3.4.2 Incidence of Drug Toxicity as a Cause of AKI

Nephrotoxicity has been estimated to contribute 8% to 60% of all cases of hospital-acquired AKI, depending on the patient population and definition of AKI (Davidman, Olson, Kohen, Leither, & Kjellstrand, 1991; Hou, Bushinsky, Wish, Cohen, & Harrington, 1983; Hui-Stickle et al., 2005; Kohli et al., 2000; Liano, Junco, Pascual, Madero, & Verde, 1998; Nash et al., 2002; Sural et al., 2000). More recently, drugs have been estimated to contribute to 19-25% of AKI cases in critically ill adults (R. L. Mehta et al., 2004; S. Uchino et al., 2005) and over 20% of the 100 most frequently prescribed medications in an adult tertiary care center were considered to be potentially nephrotoxic (Taber & Mueller, 2006).

In paediatric patient populations, exposure to nephrotoxic medications has been estimated to be the second most common cause of AKI, accounting for 16% of pediatric AKI (Hui-Stickle et al., 2005). However, there is lack of pediatric data available regarding the actual incidence of nephrotoxicity for many medications known to have deleterious effects on the kidneys.

Most studies focus solely on exposure to one medication. For example, Zappitelli et al (2011) conducted a retrospective cohort study of non-critically ill children treated with aminoglycosides (gentamicin, tobramycin or amikacin) for five or more days during their hospitalization. They estimated the incidence of AKI in this cohort of children to be 20% according to the AKIN and 33% according to the pRIFLE definition of AKI. Totapally et al (2013) conducted a retrospective cohort study of children admitted to the paediatric intensive care unit and received
vancomycin for three or more consecutive days. Forty-nine patients (17.2%) developed AKI according to the GFR criteria of the pRIFLE.

To date, the only comprehensive assessment of nephrotoxic medication-related acute kidney injury was conducted in hospitalized, non-critically ill pediatric patients (Moffett & Goldstein, 2011). The authors performed a retrospective case-control study; cases were defined as patients who developed any degree of AKI according to the pRIFLE and were matched 1:1 to controls according to age, gender and admission diagnosis. The authors collected information regarding the administration of 34 medications deemed to have nephrotoxic effects including medication exposure, total number of doses, days of medication therapy, exposure intensity, doses per therapy day and doses per admission day. Three hundred and fifty-seven case-control pairs were studied. Patients with AKI had significantly greater odds to exposure to one or more nephrotoxic medications than patients without AKI (OR=1.7, 95% CI: 1.0-2.9). Patients who developed AKI had exposure to more nephrotoxic medications for a longer period of time than their matched controls. The authors found that the use of amphotericin, cefotaxime, cisplatin, ifosfamide, piperacillin with or without tazobactam and vancomycin were independently associated with the development of AKI. When all medications were included in a multivariate regression, only vancomycin had a statistically significant association with the development of AKI. A similar assessment has not been conducted in critically ill children, and thus, the risk of nephrotoxic medication-induced AKI in critically ill children remains unknown.
2.4 Studying Drug Safety in Children

Before regulatory approval, all prescription drugs must go through rigorous study, including randomized controlled trials, to ensure efficacy and safety. Only 20% of the drugs used to treat paediatric patients have gained regulatory approval for use in these populations ("Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients," 1997).

Until recently, children and pregnant women were generally excluded from drug studies, mainly for reasons concerning the vulnerability of the patients and questions surrounding their ability to truly provide informed consent. In 1977, the American Academy of Pediatrics argued of the importance of studying drug safety in children ("American Academy of Pediatrics. Committee on Drugs. Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations," 1977). They stated that both scientifically and ethically sound studies of drugs could be conducted in paediatric populations. In fact, they argued that it was more unethical to exclude children from study as it meant that each time a child was prescribed a medication, physicians were essentially conducting an uncontrolled experiment on their patients. These guidelines were updated again in 1995 ("Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations. Committee on Drugs, American Academy of Pediatrics," 1995).

Legislation was enacted in the United States to improve drug safety knowledge in children, specifically to include children in manufacturer-led drug trials. Enacted in 2002, the Best Pharmaceuticals for Children Act encouraged drug manufacturers to conduct paediatric studies in exchange for additional patent exclusivity ("About the BCPA" 2011; Breslow, 2003; United
States Government Accountability Office Report to Congressional Committees, 2007). It also provides public funding and organizes private funding to conduct research on drug that pharmaceutical companies choose to not test in children. The Pediatric Research Equity Act was also enacted; it authorizes the FDA to require paediatric safety assessments of drugs (Thaul, 2012). It has been estimated that these pieces of legislations have allowed more drugs to be studied in children in the last decade than in the preceding five decades (McMaul & Van Hollen, 2011).

Despite these efforts, there is still a lack of randomized clinical drug trials involving paediatric patients. This is likely due to a number of factors: for example, children account for only a small percentage of drug prescriptions so the cost of conducting a randomized trial may be prohibitive for a drug company (t Jong et al., 2001). Paediatric patients may also be more difficult to recruit, as parents may be concerned about the potential effects of experimental drug on their child’s growth and development (t Jong et al., 2001). Even short-term exposure to a drug may have long-term effects; these long-term drug effects are usually unforeseeable and hard to investigate (Greenhill et al., 2003).

Even among the drugs that are licensed for paediatric use, fundamental gaps still exist in our understanding of the safety of these drugs in children. Pre-marketing drug trials, in general, recruit between a few hundred to a few thousand subjects (Strom, 2012); this sample size is likely too small to detect rare, but serious, adverse drug events (Strom, 2012).
2.4.1 Studying Acute Kidney Injury as an Adverse Drug Event:

Pharmacoepidemiology

Pharmacoepidemiology is the study of the use of and effects of drugs in large patient populations (Strom, 2012). This field has primarily concerned itself with the study of adverse drug events. Traditionally, adverse drug reactions have been studied through reports of drug-related mortality and morbidity; however, determining causation in these cases can be problematic. In the field of pharmacoepidemiology, controlled studies are performed to examine whether the adverse outcome of interest (in this case, acute kidney injury) occurs more often in exposed patients than in those unexposed to certain medications. In the case of paediatric studies, this approach is beneficial due to the smaller patient populations available for study. As children are generally excluded from pre-market drug trials, this technique can provide needed safety information regarding drug use in children.

In comparison to randomized controlled trials, pharmacoepidemiologic studies offer advantages in studying adverse drug events in children (Luo, Doherty, Cappelleri, & Frush, 2007). For example, pharmacoepidemiologic studies tend to have large sample sizes, which greatly increase the change of detecting rare adverse events. In addition, compared to randomized trials, which have rigorous inclusion and exclusion criteria, pharmacoepidemiologic studies tend to be more generalizable as they study participants in real-world settings (Luo et al., 2007). The feasibility of pharmacoepidemiological studies as increased with the development of administrative healthcare databases, based on billing claims or electronic medical records (Luo et al., 2007). The use of existing data also eliminates time and resources required for primary data collection.
This dissertation follows a pharmacoepidemiologic approach using AKI as a model to study adverse drug events in children. We will exploit the unique electronic data available from the Department of Critical Care Medicine at The Hospital for Sick Children where all clinical data for any child admitted to the PICU or CICU is charted electronically. In addition, information from other departments in the hospital, such as radiology and microbiology can be linked to the chart data based on the patients’ unique medical record number. Should this method prove successful, this method can be expanded to incorporate other ADEs of interest.
An abridged version of the following chapter has been previously published. The citation is: Slater MB, Anand V, Uleryk EM, Parshuram CS. A systematic review of RIFLE criteria in children and its application and association with measures of mortality and morbidity. Kidney International 2012; 81(8): 791-798.

Permission was received to publish in this dissertation.
3.1 Overview

The overall goal of this thesis was to evaluate the contribution of drug therapy to acute kidney injury (AKI). To accomplish this, we first needed to understand how AKI is defined in the literature. As stated in the previous chapter, we chose to focus on a specific definition of AKI known as the RIFLE. At the time of this work, three different definitions of AKI were used in the literature: the RIFLE (Bellomo et al., 2004), the pRIFLE (Akcan-Arikan et al., 2007) and the AKIN (R. L. Mehta et al., 2007). The RIFLE had been shown to capture more mild cases of acute kidney injury than the AKIN (Zappitelli et al., 2011) and the use of the AKIN classification was not shown to improve outcome prediction over the RIFLE (Bagshaw et al., 2008; Chang et al., 2010). The pRIFLE, the proposed modification to the RIFLE for use in paediatric populations (Akcan-Arikan et al., 2007), provides limited justification for the changes made to the original RIFLE (Akcan-Arikan et al., 2007). As such, the RIFLE was chosen to define AKI for the thesis work.

The objective of this chapter is to systematically review the use of the RIFLE as a definition of AKI in paediatric patient populations. We were interested in understanding how the RIFLE was operationalized in the literature and apply any lessons learned in our utilization of the criteria as an outcome. In addition, the evidence of an association between the RIFLE and outcomes of mortality and morbidity are reported. The outcomes from this systematic review were used to inform the operationalization of the RIFLE as an outcome for the remainder of the thesis work.
3.2 Introduction

Acute kidney injury (AKI) is a common adverse event in hospitalized patients, associated with increased mortality, length of stay, and resource utilization (Chertow, Burdick, Honour, Bonventre, & Bates, 2005; de Mendonca et al., 2000; F. B. Plotz et al., 2005; Ricci et al., 2008). The use of over 35 definitions of AKI has contributed to wide variation in reported incidence rates and has complicated comparisons between studies (Bellomo, Kellum, & Ronco, 2001; Bellomo et al., 2004; Ricci et al., 2008). Two main definitions of AKI have been adopted: the RIFLE (Bellomo et al., 2004) and the Acute Kidney Injury Network (AKIN) (R. L. Mehta et al., 2007) criteria, both based on common markers of kidney function. Given evidence that the RIFLE captures more mild cases of acute kidney injury than the AKIN (Zappitelli et al., 2011) and the AKIN classification does not improve outcome prediction over the RIFLE (Bagshaw et al., 2008; Chang et al., 2010), the focus of this review is on the RIFLE definition of AKI.

The RIFLE criteria were developed by an international consensus panel and are intended for use in critically ill adults (Bellomo et al., 2004). The RIFLE classifies increasing severity of acute kidney injury into 5 categories: risk (R), injury (I), and failure (F), loss of kidney function (L), and end-stage kidney disease (E). The classification is based on the magnitude and duration of changes from the patient’s normal (baseline) kidney function, assessed by glomerular filtration rate (GFR) and urine output, and the length of renal replacement therapy (RRT). When a measure of the patient’s baseline GFR is not available or is unknown, the panel suggested assuming a GFR of 75ml/min/1.73m², the lower limit of normal (Bellomo et al., 2004).

The RIFLE has been widely adopted in adult populations and is now being used as a ‘gold standard’ to validate new biomarkers of kidney function (Haase et al., 2009). However, a
systematic review of the RIFLE criteria and mortality in adults, which found increasing RIFLE severity was associated with increasing mortality, revealed that the application of the criteria was inconsistent (Ricci et al., 2008). Variations in the application of the RIFLE, particularly in the estimation methods for baseline renal function, can significantly affect the reported incidence of AKI (Siew et al., 2010; Zappitelli et al., 2008; Zavada et al., 2010).

The RIFLE criteria are now being used to describe acute kidney injury in children and a modification of the RIFLE (the pRIFLE) has been suggested for use in paediatric populations (Akcan-Arikan et al., 2007). The modifications are minor and include a focus on the estimated creatinine clearance as the measure of GFR, the threshold for the ‘Failure’ category from a serum creatinine ≥ 4 mg/100ml to an estimated creatinine clearance (eCCl) < 35 ml/min/1.73m², and increasing the time interval for the urine output criteria to 8 hours from 6 hours (Table 3.1). The increasing use of the RIFLE classification underscores the importance of consistent application and raises a need to understand if the relationships between the RIFLE criteria and mortality and morbidity found in adult patients also exist in paediatric patients. We conducted a systematic review to describe the application of the RIFLE and to assess associations between the RIFLE and measures of mortality and morbidity, specifically length of stay and measures of illness severity and kidney function, in paediatric populations.
Table 3.1: RIFLE criteria and suggested paediatric modification (pRIFLE)

<table>
<thead>
<tr>
<th>Risk</th>
<th>RIFLE (Bellomo et al., 2004)</th>
<th>Modification (pRIFLE) (Akcan-Arikan et al., 2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFR criteria</td>
<td>Urine output criteria</td>
</tr>
<tr>
<td>Risk</td>
<td>Increased creatinine x1.5 or GFR&lt;sup&gt;a&lt;/sup&gt; decrease &gt;25%</td>
<td>&lt;0.5 ml/kg/h x 6h</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased creatinine x2 or GFR decrease &gt;50%</td>
<td>&lt;0.5 ml/kg/h x 12h</td>
</tr>
<tr>
<td>Failure</td>
<td>Increased creatinine x3 or GFR decrease &gt;75% or creatinine ≥4 mg/100ml (acute rise of ≥0.5 mg/100ml dl)</td>
<td>&lt;0.3 ml/kg/h x 24h or anuria x 12h</td>
</tr>
</tbody>
</table>

**Loss**

Persistent ARF = complete loss of renal function > 4 weeks (defined as the need for renal replacement therapy (RRT) for >4 weeks)

**End stage**

End-stage renal disease (defined as the need for dialysis for >3 months)

End-stage renal disease (persistent failure >3 months)<sup>c</sup>

**RRT / Dialysis Criteria**

ARF: acute renal failure; eCCl: estimated creatinine clearance; GFR: glomerular filtration rate; RRT: renal replacement therapy

<sup>a</sup> Estimated using the Modification for Diet in Renal Disease (MDRD) formula; if no baseline measurement available, assign a lower limit of normal GFR of 75ml/min/1.73m<sup>2</sup>;

<sup>b</sup> Estimated using the Schwartz formula; if no baseline measurement available, assign 100ml/min/1.73m<sup>2</sup>

<sup>c</sup> The definitions of persistent failure were not described; it is assumed that they are the same as defined by the original RIFLE

### 3.3 Methods

A literature search was conducted in OVID SP MEDLINE and EMBASE to identify peer-reviewed publications indexed with kidney injury (or disease) that specifically mentioned the RIFLE score. The search was restricted to studies involving children (Table 3.2). Studies that
applied the RIFLE as a measure of AKI and/or described the reliability, validity, or responsiveness of the RIFLE were eligible for inclusion. Non-English studies and non-original investigations including letters, commentaries, editorials, conference abstracts, and literature reviews were excluded. Two reviewers (MS, VA) screened the abstracts independently to identify eligible studies and final inclusion was determined by consensus. If consensus could not be reached, a third reviewer (CP) determined eligibility.

**Table 3.2: Search strategy**

<table>
<thead>
<tr>
<th>OVID</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 renal insufficiency/ or kidney failure/ or kidney failure, acute/ or kidney tubular necrosis, acute/ or renal insufficiency, acute/ or Kidney Diseases/</td>
<td>94 748</td>
</tr>
<tr>
<td>2 (rifle or prifle).ti,ab.</td>
<td>653</td>
</tr>
<tr>
<td>3 1 and 2</td>
<td>204</td>
</tr>
<tr>
<td>4 Limit 4 to “all child (0 to 18 years)”</td>
<td>28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMBASE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kidney failure/ or acute kidney failure/ or acute kidney tubule necrosis/ or anuria/ or kidney cortex necrosis/ or kidney tubule necrosis/ or oliguria/ or renal osteodystrophy/ or uremia/ or kidney disease/ or kidney injury/ or (renal adj2 insufficien*).mp. or exp kidney function/ or exp dialysis/ or exp renal replacement therapy/</td>
<td>363 833</td>
</tr>
<tr>
<td>2 (rifle or prifle or (risk adj2 injury adj2 failure adj2 loss adj2 end adj2 stage adj2 disease)).ti,ab.</td>
<td>973</td>
</tr>
<tr>
<td>3 1 and 2</td>
<td>406</td>
</tr>
<tr>
<td>4 Child/</td>
<td>1 015 978</td>
</tr>
<tr>
<td>5 3 and 4</td>
<td>28</td>
</tr>
</tbody>
</table>

**TOTAL NUMBER OF STUDIES (excluding duplicates)** 45
For each article, two reviewers (MS, VA) independently abstracted data to describe: [1] the study: year of publication, study population (including inclusion and exclusion criteria), number of children studied, study design, and rationale for inclusion; [2] the application of the RIFLE: the version of the RIFLE criteria cited (the original RIFLE or the pRIFLE modification), the criteria used to determine RIFLE classification, the range of RIFLE categories reported, and the number and proportion of patients in each category; [3] how the RIFLE data were measured: the definition of baseline GFR estimate, and, if applicable, the method for handling missing baseline values; and [4] associations between the RIFLE and measures of mortality and morbidity. These included ICU and hospital mortality and length of stay, accepted illness severity scales or scores, use of mechanical ventilation, other measures of kidney function (AKIN classification and the use of dialysis or RRT), and the use of nephrotoxic medications. We did not consider associations between the RIFLE and novel markers of renal function.

The number and percentages of manuscripts with each characteristic assessed were tabulated and reported. No measures of association were presented due to significant heterogeneity in both study design and population.

### 3.4 Results

The search identified 45 articles, 12 of which met the inclusion/exclusion criteria (Ajami et al., 2010; Akcan-Arikan et al., 2007; Dennen et al., 2010; Duzova et al., 2010; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz, Bouma, van Wijk, Kneyber, & Kenkamp, 2008; Schneider et al., 2010; Washburn et al., 2008; Zappitelli et al., 2009; Zappitelli et al., 2011; Zappitelli et al., 2007) (Figure 3.1). All studies described the application of the RIFLE criteria in a paediatric
patient population and 10 (83%) described associations between the RIFLE and mortality and morbidity (Akcan-Arikan et al., 2007; Dennen et al., 2010; Duzova et al., 2010; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2009; Zappitelli et al., 2011; Zappitelli et al., 2007) (Table 3.3). The total number of patients per study ranged from 25 (Dennen et al., 2010) to 3,396 (Schneider et al., 2010), all of whom were hospital inpatients. Six studies were conducted prospectively (Ajami et al., 2010; Akcan-Arikan et al., 2007; Dennen et al., 2010; Duzova et al., 2010; Washburn et al., 2008; Zappitelli et al., 2007); the remaining six were conducted retrospectively (Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2009; Zappitelli et al., 2011). The one multicenter study included 17 centers (Duzova et al., 2010).

Patient populations varied and included, for example, all paediatric ICU admissions (Schneider et al., 2010), specific ICU patients (i.e. those with respiratory and/or cardiac failure (Akcan-Arikan et al., 2007; Frans B. Plotz et al., 2008; Washburn et al., 2008; Zappitelli et al., 2007)), and surgical patients (Dennen et al., 2010; Manrique et al., 2009; Zappitelli et al., 2009). A RIFLE severity of ‘Risk’ or higher was reported in 10% (Schneider et al., 2010) to 100% (Duzova et al., 2010) of patients (Figure 3.2).
Forty-five studies, excluding duplicates were identified by the literature search; 14 were excluded as they were conference abstracts. Other exclusions were due to language (1), lack of original research (editorials, 4; systematic review, 1) and 13 did not meet our study objectives. Overall, 12 studies met the inclusion/exclusion criteria and were included in this systematic review.

Figure 3.1: Flow diagram of included and excluded studies
Table 3.3: Summary of studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>N</th>
<th>Retrospective/prospective</th>
<th>Single/multi-center</th>
<th>Measures of association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajami (2010)</td>
<td>2010</td>
<td>Paediatric patients referred for diagnostic or interventional catheterization. Exclusion criteria mentioned but not defined.</td>
<td>80</td>
<td>Prospective</td>
<td>Single</td>
<td></td>
</tr>
<tr>
<td>Akcan-Arikan (2007)</td>
<td>2007</td>
<td>PICU patients with respiratory (defined as requiring invasive mechanical ventilation) and/or cardiac failure (defined as requiring infusions of vasoactive medications) who had indwelling urinary catheters, excluding patients with known end-stage renal disease at PICU admission or were post-renal transplant status.</td>
<td>150</td>
<td>Prospective</td>
<td>Single</td>
<td>✓</td>
</tr>
<tr>
<td>Dennen (2010)</td>
<td>2010</td>
<td>Children undergoing scheduled first time cardiopulmonary bypass for repair of congenital heart disease, excluding those with known underlying chronic kidney disease, exposure to nephrotoxins within one week of surgery, proteinuria, urinary tract infection, diabetes, unavailable baseline serum creatinine, inability to obtain consent.</td>
<td>25</td>
<td>Prospective</td>
<td>Single</td>
<td>✓</td>
</tr>
<tr>
<td>Duzova (2010)</td>
<td>2010</td>
<td>Centers identified any patient with AKI (defined as an absolute increase in SCr by either &gt;0.3 mg/dl or an increase of ≥50% from baseline or a GFR decrease ≥25% from baseline or a reduction in urine output (&lt;0.5 ml/kg for more than 8h) at the time of admission or during treatment or those who were acutely ill.</td>
<td>472</td>
<td>Prospective</td>
<td>Multicenter</td>
<td>✓</td>
</tr>
<tr>
<td>Manrique (2009)</td>
<td>2009</td>
<td>Patients undergoing congenital cardiac surgery requiring cardiopulmonary bypass.</td>
<td>395</td>
<td>Retrospective</td>
<td>Single</td>
<td>✓</td>
</tr>
<tr>
<td>Palmieri (2009)</td>
<td>2009</td>
<td>Patients with burn injury (TBSA&gt;10%) admitted to Burn ICU, excluding non-survivable burns (decision for comfort care on admission), admission for non-burn diagnosis, or burn size less than 10%.</td>
<td>123</td>
<td>Retrospective</td>
<td>Single</td>
<td>✓</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Population</td>
<td>Study Design</td>
<td>Setting</td>
<td>Source(s)</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>----------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Plotz</td>
<td>2008</td>
<td>PICU patients with respiratory failure (defined as requiring &gt;4 days mechanical ventilation).</td>
<td>Retrospective</td>
<td>Single</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Schneider</td>
<td>2010</td>
<td>All patients admitted to PICU excluding those with preexisting chronic renal insufficiency, end-stage renal disease, or admission for renal transplantation.</td>
<td>Retrospective</td>
<td>Single</td>
<td>3396</td>
<td></td>
</tr>
<tr>
<td>Washburn</td>
<td>2008</td>
<td>PICU patients requiring mechanical ventilation and indwelling bladder catherization, excluding patients with known end-stage renal disease at PICU admission or were post-renal transplant status (same as Akcan-Arikan(2007)). Patients with less than 2 SCr levels or those with no urine specimens were also excluded.</td>
<td>Prospective</td>
<td>Single</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Zappitelli</td>
<td>2007</td>
<td>PICU patients requiring mechanical ventilation and indwelling bladder catherization, excluding patients with known end-stage renal disease at PICU admission or were post-renal transplant status (same as Akcan-Arikan(2007)).</td>
<td>Prospective</td>
<td>Single</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Zappitelli</td>
<td>2009</td>
<td>Patients undergoing open chest surgery excluding patients with no SCr measured during their ICU stay.</td>
<td>Retrospective</td>
<td>Single</td>
<td>390</td>
<td></td>
</tr>
<tr>
<td>Zappitelli</td>
<td>2011</td>
<td>Patients hospitalized in non-intensive care units and received gentamicin, tobramycin, or amikacin for ≥5 days, excluding patients with primary diagnoses of genitourinary or renal disorders at hospital admission.</td>
<td>Retrospective</td>
<td>Single</td>
<td>557</td>
<td></td>
</tr>
</tbody>
</table>

GFR: glomerular filtration rate; ICU: intensive care unit; PICU: pediatric intensive care unit; SCr: serum creatinine; TBSA: total body surface area
Figure 3.2: Reported incidence and distribution of RIFLE-assessed AKI

The rates of AKI reported in each study ranged from 10% to 100% of patients. The distribution of severity is also shown and varies across studies. Dennen et al (2010) did not report RIFLE categories separately and thus is omitted.

3.4.1 Application of the RIFLE

Four studies (25%) cited using the original RIFLE (Ajami et al., 2010; Dennen et al., 2010; Manrique et al., 2009; Schneider et al., 2010) and the remaining 8 (75%) referenced the proposed paediatric modification (Akcan-Arik et al., 2007; Duzova et al., 2010; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Washburn et al., 2008; Zappitelli et al., 2009; Zappitelli et al., 2011; Zappitelli et al., 2007). All studies used the GFR criteria to define and classify acute kidney injury (Table 3.4) and five used the GFR criteria in combination with the urine
output criteria (Akcan-Arikan et al., 2007; Duzova et al., 2010; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008). No study relied solely on urine output to classify AKI. One study (8%) only reported AKI as defined by a RIFLE category of ‘R’ or higher (Dennen et al., 2010), 10 studies (83%) reported the first three clinical categories (Risk, Injury, and Failure) (Ajami et al., 2010; Akcan-Arikan et al., 2007; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Washburn et al., 2008; Zappitelli et al., 2009; Zappitelli et al., 2011; Zappitelli et al., 2007) and one study (8%) used all of the RIFLE categories (Duzova et al., 2010).

3.4.1.1 Missing Data

In nine studies (75%), it was unclear if patients were excluded if they were missing data necessary to determine RIFLE classification and, in the event data were missing, it was unclear how this was handled (Ajami et al., 2010; Akcan-Arikan et al., 2007; Dennen et al., 2010; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2011; Zappitelli et al., 2007). Two studies purposefully excluded patients: Zappitelli et al (2009) stated that patients with no serum creatinine measurements during the study period were excluded and Washburn et al (2008) excluded patients with less than 2 serum creatinine measurements. It is unlikely that Duzova et al (2010) purposefully excluded patients as they state that only 423 (89.6%) of the 472 patients enrolled in the study had a RIFLE classification available.
Table 3.4: Summary of RIFLE application

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Tool cited (RIFLE, pRIFLE)</th>
<th>Criteria used (GFR, UO, both)</th>
<th>GFR method (eCCl, Cr)</th>
<th>GFR Criteria</th>
<th>Method for missing baseline creatinine</th>
<th>Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajami (2010)</td>
<td>2010</td>
<td>RIFE</td>
<td>GFR</td>
<td>eCCl (Schwartz)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>N/A</td>
</tr>
<tr>
<td>Akcan-Arikan (2007)</td>
<td>2007</td>
<td>pRIFLE</td>
<td>Both</td>
<td>eCCl (Schwartz)</td>
<td>Lowest SCr in 3m proceeding ICU admission</td>
<td>Assigned baseline eCCl=100ml/min/1.73m²</td>
<td>x8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Indwelling Foley catheter an inclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Dennen (2010)</td>
<td>2010</td>
<td>RIFE</td>
<td>GFR</td>
<td>Cr</td>
<td>Pre-operative measurement (not defined more specifically)</td>
<td>Patients with missing baseline values were excluded.</td>
<td>N/A</td>
</tr>
<tr>
<td>Duzova (2010)</td>
<td>2010</td>
<td>pRIFLE</td>
<td>Both</td>
<td>eGFR (estimation method not specified)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>x8 hours</td>
</tr>
<tr>
<td>Palmieri (2009)</td>
<td>2009</td>
<td>pRIFLE</td>
<td>Both</td>
<td>eCCl (Schwartz)</td>
<td>eCCl calculated using SCr within 3m prior to admission</td>
<td>Assigned eCCl=120ml/min/1.73m²</td>
<td>x8 hours</td>
</tr>
<tr>
<td>Plotz (2008)</td>
<td>2008</td>
<td>pRIFLE</td>
<td>Both</td>
<td>eCCl (Schwartz)</td>
<td>SCr within 3m of ICU admission</td>
<td>Assigned eCCl=100ml/min/1.73m²</td>
<td>x8 hours</td>
</tr>
</tbody>
</table>

Timing: x6 hours, x8 hours
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Systematic Kidney Injury Scale (SKIN)</th>
<th>GFR</th>
<th>SCr</th>
<th>Methodology</th>
<th>Norms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider (2010)</td>
<td>2010</td>
<td>RIFLE GFR Cr</td>
<td>Most recent documented SCr within 6m prior to ICU admission</td>
<td>Assigned an age/gender appropriate high-end normal SCr</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Washburn (2008)</td>
<td>2008</td>
<td>pRIFLE GFR eCCl (Schwartz)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Zappitelli (2007)</td>
<td>2007</td>
<td>pRIFLE GFR eCCl (Schwartz)</td>
<td>Lowest known SCr value during the 3m prior to study enrollment.</td>
<td>Assigned eCCl=120ml/min/1.73m²</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

For patients with no known baseline SCr and PICU admission eCCl > 120ml/min/1.73m², baseline eCCl was recorded as admission eCCl.

Zappitelli (2009) | 2009 | pRIFLE GFR Cr | Pre-operative SCr (within 1w of surgery) or lowest in previous month | Assigned minimum norms for age and gender | N/A | N/A |

Zappitelli (2011) | 2011 | pRIFLE GFR eCCl (Schwartz) | Lowest SCr within 3 months prior to treatment initiation | Assigned eCCl=120ml/min/1.73m² | N/A | N/A |

Cr: creatinine; eCCl: estimated creatinine clearance; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; SCr: serum creatinine; UO: urine output
3.4.1.2 GFR Criteria

The GFR criteria were assessed by relative changes in estimated creatinine clearance (n=8) (Ajami et al., 2010; Akcan-Arikan et al., 2007; Duzova et al., 2010; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Washburn et al., 2008; Zappitelli et al., 2011; Zappitelli et al., 2007), changes in serum creatinine (n=3) (Dennen et al., 2010; Schneider et al., 2010; Zappitelli et al., 2009), or were not specified (n=1) (Manrique et al., 2009). Of those that used eCCl, 7 (88%) specified that the estimated creatinine clearance was calculated using the Schwartz formula (Ajami et al., 2010; Akcan-Arikan et al., 2007; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Washburn et al., 2008; Zappitelli et al., 2011; Zappitelli et al., 2007); one study did not specify the estimation method (Duzova et al., 2010). The Schwartz method requires the patient’s height along with a serum creatinine measurement (Schwartz, Haycock, Edelmann, et al., 1976). No study discussed the availability or accuracy of height measurements or how the absence of these data was managed.

Definitions of the baseline measurement of renal function varied; 5 studies used creatinine measured within 3 months of admission or study initiation (Akcan-Arikan et al., 2007; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Zappitelli et al., 2011; Zappitelli et al., 2007), one used the most recent measure within 6 months of admission (Schneider et al., 2010), and two used pre-operative serum creatinine measures: one within one week of surgery or the lowest measure available in the month prior to surgery (Zappitelli et al., 2009), the other did not specify the time period (Dennen et al., 2010). Four studies did not specify the baseline definition (Ajami et al., 2010; Duzova et al., 2010; Manrique et al., 2009; Washburn et al., 2008).
Missing baseline GFR values were managed as follows: five assigned values of either 100ml/min/1.73m$^2$ (Akcan-Arikan et al., 2007; Frans B. Plotz et al., 2008) or 120ml/min/1.73m$^2$ (Palmieri et al., 2009; Zappitelli et al., 2011; Zappitelli et al., 2007) for estimated creatinine clearance. Two studies used age- and gender-adjusted normal values for missing baseline creatinine values; one used high-end normal values (Schneider et al., 2010) and the other used the lower limit of normal (Zappitelli et al., 2009). Four studies did not specify how missing baseline GFR values were accounted for (Ajami et al., 2010; Duzova et al., 2010; Manrique et al., 2009; Washburn et al., 2008) and one study excluded patients with missing baseline values (Dennen et al., 2010).

3.4.1.3 Urine Output Criteria

Of the five studies that applied the urine output criteria (Akcan-Arikan et al., 2007; Duzova et al., 2010; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008), only one study included patients with indwelling urinary catheters (Akcan-Arikan et al., 2007). Urine output was assessed in 6 hour intervals according to the RIFLE in one study (Manrique et al., 2009); four studies used 8 hour intervals, according to the pRIFLE (Akcan-Arikan et al., 2007; Duzova et al., 2010; Palmieri et al., 2009; Frans B. Plotz et al., 2008).

3.4.2 Associations Between the RIFLE and Measures of Mortality and Morbidity

Ten studies assessed relationships between the RIFLE and measures of mortality, length of stay, and illness severity (Akcan-Arikan et al., 2007; Dennen et al., 2010; Duzova et al., 2010; Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2009; Zappitelli et al., 2011; Zappitelli et al., 2007) (Table 3.5). To
maintain consistency and comparability of results across studies, only unadjusted analyses are presented below.

3.4.2.1 Mortality

Six studies evaluated the association between mortality and RIFLE-assessed AKI (Akcan-Arikan et al., 2007; Duzova et al., 2010; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2007). Two studies showed that AKI, defined as a RIFLE severity of ‘Risk’ or higher, was significantly associated with increased mortality (Frans B. Plotz et al., 2008; Schneider et al., 2010); one study found this relationship to be borderline significant ($p=0.057$) (Palmieri et al., 2009). Two studies found a non-significant relationship when the RIFLE was dichotomized in this manner, but found significant increases in mortality when using different cut points (i.e. ‘Injury’ or higher) (Akcan-Arikan et al., 2007; Zappitelli et al., 2007). Of the four studies that assessed mortality across RIFLE strata (Duzova et al., 2010; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010), two showed significant differences (Palmieri et al., 2009; Schneider et al., 2010) while the other two studies found no significant difference in mortality rates across RIFLE categories (Duzova et al., 2010; Frans B. Plotz et al., 2008).

3.4.2.2 Length of Stay (LOS)

Seven studies evaluated the association between RIFLE-assessed AKI and length of stay (LOS) (Akcan-Arikan et al., 2007; Dennen et al., 2010; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2009; Zappitelli et al., 2011); five studies showed that AKI, defined as ‘Risk’ or higher, was significantly associated with longer hospital LOS (Akcan-Arikan et al., 2007; Dennen et al., 2010; Palmieri et al., 2009;
Zappitelli et al., 2009; Zappitelli et al., 2011) and longer ICU stay (Dennen et al., 2010; Palmieri et al., 2009; Schneider et al., 2010; Zappitelli et al., 2009), though two studies showed no significant relationship with ICU LOS (Akcan-Arikan et al., 2007; Frans B. Plotz et al., 2008). Two studies assessed the relationship between LOS and RIFLE strata and no significant association was found for hospital (Palmieri et al., 2009) or ICU LOS (Palmieri et al., 2009; Schneider et al., 2010).

3.4.2.3 Illness Severity

Five studies compared the RIFLE with a total of four validated illness severity scores (Akcan-Arikan et al., 2007; Palmieri et al., 2009; Schneider et al., 2010; Zappitelli et al., 2009; Zappitelli et al., 2007). Three studies reported associations between the Pediatric Risk of Mortality Score (PRISM) (Akcan-Arikan et al., 2007; Palmieri et al., 2009; Zappitelli et al., 2007); Akcan-Arikan et al found a non-significant association between a dichotomous measure of AKI and a significant increase in PRISM scores across RIFLE strata (Akcan-Arikan et al., 2007) while Palmieri et al found a significant association of AKI with PRISM but no significant difference across RIFLE strata (Palmieri et al., 2009). Zapitelli et al did show that PRISM scores increased progressively with increasing RIFLE (Zappitelli et al., 2007). Pediatric Index of Mortality (PIM2) scores were higher in patients presenting with AKI at ICU admission (Schneider et al., 2010). Surgical severity, as measured by the Aristotle score, was significantly higher in patients with AKI, but severity according to the Risk Adjustment in Congenital Heart Surgery (RACHS-1) score was not associated with RIFLE (Zappitelli et al., 2009).
Table 3.5: Summary of associations between the RIFLE and measures of mortality and morbidity

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<td>Aristotle score</td>
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AKIN: Acute Kidney Injury Network; ICU: intensive care unit; PIM: Pediatric Index of Mortality; PRISM: Pediatric Risk of Mortality; RRT: renal replacement therapy

Note: Significant association denoted by +; non-significant association denoted by -. Blank means that this association was not reported.
Five studies assessed the relationship between RIFLE and length of mechanical ventilation (Manrique et al., 2009; Palmieri et al., 2009; Frans B. Plotz et al., 2008; Schneider et al., 2010; Zappitelli et al., 2009); significantly longer lengths of mechanical ventilation in patients with AKI were reported by 3 studies (Palmieri et al., 2009; Schneider et al., 2010; Zappitelli et al., 2009); the remaining studies found non-significant associations (Manrique et al., 2009; Frans B. Plotz et al., 2008). No significant difference across RIFLE categories was found (Palmieri et al., 2009).

3.4.2.4 Measures of Kidney Function

One study compared the RIFLE GFR criteria with the AKIN measurement for AKI and found a high level of agreement between the two methods (84.4%) (Zappitelli et al., 2011).

Four studies assessed the relationship between RIFLE and dialysis use (Duzova et al., 2010; Frans B. Plotz et al., 2008; Zappitelli et al., 2009; Zappitelli et al., 2007). Two studies only assessed a dichotomous measure of AKI and reported that dialysis use and renal replacement therapy are significantly higher in patients with AKI (Frans B. Plotz et al., 2008; Zappitelli et al., 2009). The remaining studies both reported an increase in dialysis use across RIFLE strata, though these trends were not significant (Duzova et al., 2010; Zappitelli et al., 2007).

3.4.2.5 Risk of Kidney Injury

The relationship between use of nephrotoxic medications and the RIFLE was evaluated in three studies (Palmieri et al., 2009; Zappitelli et al., 2009; Zappitelli et al., 2011); two studies showed that patients with AKI were treated significantly longer with aminoglycosides than patients without AKI (Zappitelli et al., 2009; Zappitelli et al., 2011). Palmieri et al found that
the proportion of patients treated with nephrotoxic medications (aminoglycosides or vancomycin) was similar, though non-significant, in patients with and without AKI; however, the proportion significantly increased with increasing RIFLE severity (Palmieri et al., 2009).

3.5 Discussion

We performed a systematic review of the application of the RIFLE classification of acute kidney injury and its association with measures of mortality and morbidity in paediatric patients. Twelve studies met our inclusion criteria. Overall, we found that the methods used to determine the RIFLE classification were incompletely described. Only two of the twelve studies provided sufficient details to confirm the measurement of the RIFLE items were consistent with the cited method (Akcan-Arikan et al., 2007; Frans B. Plotz et al., 2008).

Second, the application of the individual criteria varied significantly between studies, including exclusion of the urine output criteria and differences in the operationalization of the GFR criteria, baseline GFR definitions, and methods for estimating missing baseline values. These findings suggest that paediatric populations may be vulnerable to the same measurement-induced variability seen in adult populations (Ricci et al., 2008); for example, of the 24 studies included in Ricci et al.’s systematic review on the relationship between the RIFLE and mortality, only 12 included both the GFR and urine output criteria to define RIFLE-based AKI. Consistent application of the RIFLE criteria is crucial to provide a valid estimate of AKI within the population of interest as the estimated incidence of AKI can be significantly influenced by various applications of the criteria (Siew et al., 2010; Zavada et al., 2010). For example, different methods for estimating baseline GFR status have been
shown to change the estimated incidence of AKI from 12% to 88% in critically ill children and 5% to 43% in non-critically ill children (Zappitelli et al., 2008). In addition, heterogeneity in the application of the RIFLE prevents meaningful comparison of the rates of AKI between different study populations. The proposed modification to the RIFLE for use in paediatric populations further adds to this variability, with limited justification provided for the changes made to the original RIFLE (Akcan-Arikan et al., 2007). Modification of the urine output assessment from a 6 hour to an 8 hour interval may be illustrative of pragmatic customization of the RIFLE due to institutional practice or difficulty with measurement accuracy. Only 58% of studies utilized the urine output criteria, perhaps because of the difficulty of timed urine collection in patients who are not catheterized. Authors may have overcome logistic challenges by customizing the RIFLE criteria to better fit with existing clinical data. While customization may serve the immediate needs of individual studies, it limits the advantages of a common measure and may illustrate a lack of consensus surrounding the application of the RIFLE in children. This issue is not limited to paediatric populations as modifications of the RIFLE have also been proposed for adult patients. For example, Herget-Rosenthal et al proposed that serum cystatin C may be a useful biomarker to improve the sensitivity of the RIFLE criteria (Herget-Rosenthal et al., 2004) and Tallgren et al included it within the GFR criteria when they applied the RIFLE to assess AKI in patients undergoing open abdominal aortic surgery (Tallgren et al., 2007). The issue of customization highlights the importance of clearly outlining the definitions and measurement processes used when defining RIFLE-based AKI.

Third, unlike in adult studies (Ricci et al., 2008) we found inconsistent relationships between the RIFLE classification and measures of mortality and morbidity in children. Studies reported discordant results between increasing RIFLE severity and mortality, length of stay,
illness severity, and measures of kidney function. These discrepancies may be due to sample size limitations, heterogeneity between the study populations, or differences in the application of the RIFLE. Sample size is an obvious limitation given the relative rarity of AKI outcomes, such as mortality, in paediatric populations. A recent review focusing on adult studies with a minimum of 1,000 patients showed consistent, significant associations between the RIFLE and mortality (Srisawat, Hoste, & Kellum, 2010). Two studies described their methodology in enough detail to determine that they followed the methodology exactly as cited (Akcan-Arikan et al., 2007; Frans B. Plotz et al., 2008); the reported associations with mortality were not consistent, though both studies found no significant association between AKI and increased ICU LOS. Three studies utilized the same patient population but were not consistent in their application of the pRIFLE (Akcan-Arikan et al., 2007; Washburn et al., 2008; Zappitelli et al., 2007). Washburn et al (2008) did not report any associations of interest for this review, however, both Akcan-Arikan et al (2007) and Zappitelli et al (2007) showed significant increases in mortality in patients with AKI as well as significantly higher PRISM scores with increasing RIFLE severity. From these limited results, it appears that similar associations are seen when the RIFLE is applied consistently and it may be that differences in RIFLE application do not affect measures of association within similar patient populations. It should be noted that as most studies did not capture the full spectrum of RIFLE severity we cannot evaluate the associations between measures of mortality and morbidity within the highest severity levels of the measure (‘Loss’ and ‘End-stage’). However, it may be that the long-term observation required for these grades of AKI severity was not applicable in studies focused on hospital outcomes. In addition, some of the variability in the reported associations may be due to several other confounding factors, such
as illness severity. We chose to only report unadjusted results as studies did not control for the same factors and adjusted results were thus not comparable across studies.

While associations between the RIFLE and measures of mortality and morbidity are useful, they are not demonstrative of the RIFLE’s ability to accurately reflect acute kidney injury. Thus, the RIFLE may be a good measure of illness severity, but may not truly capture the presence of AKI. Ideally, the RIFLE would be compared with a ‘gold standard’ measure of acute kidney injury. However, unlike chronic kidney disease, no ‘gold standard’ diagnostic test exists for the diagnosis and severity classification of acute kidney injury; it is based on a combination of patient symptoms, clinical tests, and clinical judgment. Comparison of the RIFLE with the AKIN classification confirms these tools are unsurprisingly correlated (Zappitelli et al., 2011; Zappitelli et al., 2008), a comparison limited in value as both measures are creatinine-based. Substitute measures of kidney function have been assessed, such as the relationship between the RIFLE and renal replacement therapy (Duzova et al., 2010; Frans B. Plotz et al., 2008; Zappitelli et al., 2009). However, the value of these assessments is limited as the use of renal replacement therapy is captured within the RIFLE definition and non-renal indications for dialysis also exist.

The widespread adoption of the RIFLE criteria is reflective of its collaborative development and the pragmatic use of the most common measurements of renal function: creatinine and urine output. The continued use of the RIFLE classification will be strengthened by a consistent approach to the application of RIFLE criteria, including the handling of missing baseline values, the methods used for the GFR criteria, and the duration over which urine output is measured. It is likely that the same variability in application is also prevalent in the use of the AKIN staging of acute kidney injury, though this was outside the scope of this
review. While customization of the RIFLE may be necessary due to specific needs of certain populations under study, we suggest that a clear description of all methodology used to classify RIFLE-based AKI will allow for easier comparison between studies and patient populations. Further work is also required to fully understand the relationship between the RIFLE and measures of mortality and morbidity in children.

Overall, our results suggest that the use of the RIFLE to assess AKI in children supports the concept of a standardized measure of acute kidney injury severity. However, inconsistencies in the use of the RIFLE have not facilitated the comparison of rates and outcomes of AKI in children. While no single definition or classification of a complex disease such as acute kidney injury will be perfect, a consensus must be reached as to its operationalization.
Chapter 4  Risk Factors of Acute Kidney Injury in Critically Ill Children
4.1 Overview

The overall goal of this work was to evaluate the contributions of drug therapy to acute kidney injury (AKI). The previous chapter systematically reviewed the use of the RIFLE as a definition of AKI in paediatric patient populations and was used to inform the operationalization of the RIFLE as a definition of AKI, the outcome of interest, for the remainder of the thesis work.

The next step of the thesis work is to quantify the characteristics and clinical factors that place paediatric patients at higher risk for developing AKI. This chapter presents a cohort study of critically ill children that estimates the incidence of AKI occurring during ICU treatment. In addition, this cohort analysis assesses the factors associated with the development of AKI occurring during ICU admission. These risk factors occur prior to ICU admission (e.g. age, gender) and during the patient’s ICU stay (e.g. organ dysfunction, nephrotoxic drug therapy). The results from the systematic review and this study will then be combined to evaluate the association between specific medications and the development of AKI, controlling for underlying differences in risk (Chapter 5).

4.2 Introduction

Acute kidney injury (AKI), a common adverse event in hospitalized patients, is associated with increased mortality, morbidity and resource use (Chertow et al., 2005; de Mendonca et al., 2000; F. B. Plotz et al., 2005; Ricci et al., 2008; Toth et al., 2012). Recent studies have estimated the incidence of AKI in hospitalized children to range from 9% to 83% (Hassinger
et al., 2012; P. Mehta et al., 2012; Morgan et al., 2013; M. B. Slater, Anand, Uleryk, & Parshuram, 2012; Toth et al., 2012) and our systematic review of AKI in children (Chapter 3) reported incidences from 10% to 83% (M. B. Slater et al., 2012). Variability among incidence estimates can be attributed to differences in both the patient populations studied and in the definition of AKI (M. B. Slater et al., 2012).

Critically ill patients are at risk of developing AKI (S. L. Goldstein & Chawla, 2010; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). In addition, they may be predisposed to developing AKI based on their underlying medical conditions or treatments before admission to the intensive care unit (ICU). Conversely, fluctuating medical status and treatments received during ICU admission may also increase the risk of developing AKI. Previous studies evaluating risk factors for AKI in children have been limited by a focus on specific patient populations, such as children (Aydin et al., 2012) or neonates (Morgan et al., 2013) undergoing cardiac surgery and extremely low birth weight infants (Viswanathan, Manyam, Azhibekov, & Mhanna, 2012), and by small sample size, limiting the power of analyses to detect clinically important risk factors. In a 2007 study of 985 critically ill children, older age (greater than 12 years), thrombocytopenia, hypoxemia, hypotension and coagulopathy were significant independent risk factors of AKI (Bailey et al., 2007).

Given that patients who develop AKI have an increased risk of mortality (Barletta & Bunchman, 2004; Bresolin et al., 2009; Ricci et al., 2008), identifying risk factors of AKI may allow for prospective risk assessment and improved patient outcomes. The objectives of this study were to estimate the incidence of paediatric AKI occurring during ICU treatment.
and to determine what factors were associated with the development of AKI occurring during ICU admission.

### 4.3 Methods

We performed a secondary analysis of electronic health data from a cohort of critically ill children admitted to the ICU of a university-affiliated, paediatric academic center. Eligible ICU admissions were the first ICU admission to the Paediatric Intensive Care Unit (PICU) or Cardiac Intensive Care Unit (CICU) at The Hospital for Sick Children (HSC) in Toronto, Ontario between January 2006 and June 2009. Patients were excluded if they had an admission diagnosis of renal disease (i.e., known primary renal failure, post-renal transplant, or chronic renal failure), drug overdose, tumor lysis syndrome, haemolytic uraemic syndrome (conditions with known renal complications) or methylmalonic acidemia or urea cycle defect (metabolic conditions treated with dialysis). In addition, patients who were less than two weeks of age were excluded to minimize the impact of maternal creatinine on measured creatinine levels in the child (Guignard & Drukker, 1999; Miall et al., 1999). Patients who were admitted to the ICU for less than six hours were also excluded as these patients tend to be admitted for observation or minor procedures only. In addition, patients with no creatinine or urine output measurements during their ICU admission were also excluded as they were missing necessary measurements to assess renal function. All subsequent ICU admissions were also excluded; thus only one ICU admission for each patient was included in the study population.
The study utilized the unique electronic data available from the Department of Critical Care Medicine at The Hospital for Sick Children. All clinical data for any child admitted to the PICU or CICU is charted electronically (CIMS, Sunrise Clinical Documentation, Eclipsys). Radiology procedures, microbiology data, admission diagnoses and creatinine values and drug administrations prior to ICU admission were accessed through linkages, based on the patients’ unique medical record number, to other electronic data systems within the hospital.

The RIFLE criteria (Bellomo et al., 2004) were used to define a dichotomous measure for the occurrence of AKI: any patient who reached a RIFLE severity of ‘Risk’ or higher (a 1.5 increase in serum creatinine from baseline or a urine output of <0.5ml/kg/hour for 6 hours) was considered to have AKI. To assess AKI occurring due to exposures within the ICU environment, the baseline measure of renal function was slightly modified from the RIFLE, defined as the first serum creatinine measurement within 24 hours of ICU admission. If this was not available, according to the RIFLE we then used the most recent creatinine measurement within 3 months prior to ICU admission; otherwise the mean age- and sex-adjusted norm (Schwartz, Haycock, & Spitzer, 1976) was used.

Possible risk factors of AKI were identified through literature review and consultation with clinical experts. Candidate risk factors were classified into two groups: baseline risk factors were those existing at the time of ICU admission and in-ICU risk factors were those occurring during the ICU stay. The 13 baseline risk factors were: age at ICU admission; gender; unplanned ICU admission; admission type (surgical admission, categorized as either cardiac or non-cardiac, or medical admission); ICD-10 admission diagnoses (World Health Organization, 2010) of circulatory disease (I00-I99), endocrine disease (E00-E99), infectious disease (A00-B99), injury (S00-T98), neoplasm (C00-D48), nervous system disease (G00-
G99), or respiratory disease (J00-J99); and Pediatric Risk of Mortality (PRISM) score
(Pollack, Ruttimann, & Getson, 1988). The administration of nephrotoxic medication prior
to ICU admission was collected for those patients admitted to the ICU from within the
hospital; prior nephrotoxic drug administration was classified as unknown for patients
admitted directly to the ICU from another hospital.

The 13 risk factors during ICU care were: the presence of Systemic Inflammatory Response
Syndrome (SIRS) (B. Goldstein, Giroir, & Randolph, 2005), sepsis (B. Goldstein et al.,
2005), shock (Leteurtre et al., 1999), septic shock, organ dysfunction (cardiovascular,
neurologic, haematologic, respiratory), mechanical ventilation, the use of extracorporeal
membrane oxygenation (ECMO), the administration of intravenous radiologic contrast and
nephrotoxic medication administration. The presence of cardiovascular, neurologic,
haematologic, hepatic and respiratory organ dysfunction was defined as a paediatric logistic
organ dysfunction (PELOD) score (Leteurtre et al., 2003) of one or more for each system.
The administration of a nephrotoxic medication was captured as a binary variable indicating
the administration of one or more medications defined as being nephrotoxic. Each risk factor
was assessed until the development of AKI or death or discharge from the ICU.

4.3.1 Identification of Nephrotoxic Medications

All medications administered in the ICU were assessed for nephrotoxicity through a review
of adverse reactions noted in the drug monographs in the hospital formulary, the
Compendium of Pharmaceuticals and Specialties (Compendium of Pharmaceuticals and
Specialties 2013, 2012), the Pediatric Dosage Handbook (Taketomo, Hodding, & Kraus,
2012). Any medication with explicit or implied renal effects was identified; this resulted in
82 medications categorized as potentially nephrotoxic. To confirm this initial list of
medications, we used a Delphi process (Fink, Kosecoff, Chassin, & Brook, 1984) whereby we consulted with the following clinical experts: a paediatric intensivist, a paediatric pharmacologist and two paediatric pharmacists. For each medication, the experts were asked to rate the likelihood and severity of AKI resulting from use of the medication. The likelihood of AKI was assessed through the question ‘Assuming it is used as recommended, what is the likelihood of a patient developing kidney injury from exposure to this medication?’ Experts were provided 7 response options: none; very low (<1%), low (1-5%), medium (5-10%), high (10-20%), very high (>20%) and unknown. Experts were also asked ‘How would you classify the severity of kidney injury caused by this medication?’ and were given the following response options: low, moderate, severe, unknown and not applicable (for medications rated as having no likelihood of kidney injury). The first round of responses were tabulated and a second round of questionnaires, which incorporated the results from the first round, were sent to the experts. The responses to the first round of questions were presented as the frequency of responses, represented by the number of dots beside each response option (Table 4.1). The results from the second round were tabulated and medications were considered to be nephrotoxic if at least 50% of responses (i.e. two or more of the four panel members) indicated that the likelihood of kidney injury was medium or higher or the severity of AKI was moderate or more severe.

The Delphi process resulted in 29 medications identified as having important nephrotoxic effects: acyclovir, amikacin, amphotericin, captopril, carboplatin, cidofovir, cisplatinum, cyclophosphamide, cyclosporine, enalapril, enalaprilat, ethacyrnic acid, flucytosine, foscarnet, furosemide, ganciclovir, gentamicin, hydrochlorothiazide, ibuprofen, ifosfamide, indomethacin, ketorolac, methotrexate, penicilllin, ramipril, sirolimus, tacrolimus, tobramycin, and vancomycin.
Table 4.1: Example of second round of expert opinion survey

<table>
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<th>Medication Name</th>
<th>1. Assuming it is used as recommended, what is the likelihood of a patient developing kidney injury from exposure to this medication?</th>
<th>2. How would you classify the severity of kidney injury caused by this medication?</th>
</tr>
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<tr>
<td>6 MERCAPTOPURINE</td>
<td>[ ] None [ ] Very low (&lt;1%) [ ] Low (1-5%) [ ] Medium (5-10%) [ ] High (10-20%) [ ] Very high (&gt;20%) [ ] Don’t know</td>
<td>[ ] Low [ ] Moderate [ ] Severe [ ] Don’t know N/A</td>
</tr>
<tr>
<td>ACYCLOVIR</td>
<td>[ ] None [ ] Very low (&lt;1%) [ ] Low (1-5%) [ ] Medium (5-10%) [ ] High (10-20%) [ ] Very high (&gt;20%) [ ] Don’t know</td>
<td>[ ] Low [ ] Moderate [ ] Severe [ ] Don’t know N/A</td>
</tr>
</tbody>
</table>
Descriptive statistics, including median and interquartile range (IQR) for continuous variables and proportions for categorical data, were used to characterize the demographic and clinical composition of the study population. The proportion of patients with creatinine and urine output measurements available during their ICU stay were reported, calculated as the number of patients with at least one measurement available by the total number of patients in the ICU on a given day. The first ICU day was defined as the 24-hour period beginning at ICU admission and subsequent ICU days were referenced according to the admission time, rather than defined according to calendar days. Exploratory analyses were performed to evaluate the impact of different definitions of baseline creatinine and the exclusion of components of the RIFLE classification on the estimated incidence of AKI. Agreement between estimated AKI severity according to varying baseline definitions was estimated using a kappa statistic. A weighted kappa, which weights agreement according to how close the categories are (Cohen, 1968), was used in order to better reflect the fact that disagreement between the adjacent categories ‘Risk’ and ‘Injury’ severity levels is different than disagreement between ‘Risk’ and ‘Failure’.

Bivariate analyses of the association between risk factors and the development of AKI were conducted using chi-square tests or, for continuous variables, the Wilcoxon-rank sum test. Any candidate risk factor with a bivariate significance level of 0.2 or smaller was eligible for inclusion in the multivariable logistic regression model. Spearman correlations and variance inflation factors (VIF) were calculated to assess multicollinearity. For variables with a VIF greater than 5 (O'Brien, 2007) or pairs of variables with correlations greater than 0.5, clinical judgment was used to determine which were included in the multivariable model. Backward
stepwise regression was performed to find the most parsimonious multivariable model. All analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC).

This study received approval from The Hospital for Sick Children’s Research Ethics Board.

4.4 Results

Between January 1, 2006 and June 30, 2009, there were 3,865 children admitted to the ICU at The Hospital for Sick Children in Toronto, Canada who were eligible for further study (Figure 4.1). The median age was 4.4 years (IQR=11.1); 30% of patients were under 12 months of age, 23% between 13 months and 5 years, 20% between 6 and 11 years, and 28% were between 12 and 18 years of age (Table 4.2). Forty-four percent of the admitted patients were female. Approximately 49% of ICU admissions were unplanned; 55% of patients were admitted to the ICU post-operatively while 18% were admitted directly to the ICU from another hospital. The median length of stay was of 2 days (IQR=3) and the ICU mortality rate was 3.3%.
During the study period, there were 6,326 admissions to the ICU; 24.5% of these were repeat admissions and were excluded. Also excluded were 654 patients who were less than 2 weeks old, 64 patients who had an ICU stay of less than 6 hours, leaving 4,056 patients. Of these, 173 had pre-existing renal conditions and a further 18 had no creatinine or urine output measurements available. Once these patients were excluded, the study population consisted of 3,865 patients.

**Figure 4.1: Definition of study population**
Table 4.2: Description of study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
</tr>
<tr>
<td>Term neonate (≤27 days)</td>
<td>68 (1.8)</td>
</tr>
<tr>
<td>Infant (28 days – 12 months)</td>
<td>1096 (28.4)</td>
</tr>
<tr>
<td>Toddler (13 months – 2 years)</td>
<td>326 (8.4)</td>
</tr>
<tr>
<td>Early childhood (2 – 5 years)</td>
<td>547 (14.2)</td>
</tr>
<tr>
<td>Middle childhood (6 – 11 years)</td>
<td>755 (19.5)</td>
</tr>
<tr>
<td>Early adolescence (12 – 18 years)</td>
<td>1073 (27.8)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1701 (44.0)</td>
</tr>
<tr>
<td>Male</td>
<td>2164 (56.0)</td>
</tr>
<tr>
<td><strong>Unplanned admission</strong></td>
<td>1887 (48.8)</td>
</tr>
<tr>
<td>Admitted to ICU from</td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>509 (13.2)</td>
</tr>
<tr>
<td>Hospital ward</td>
<td>553 (14.3)</td>
</tr>
<tr>
<td>Operating room</td>
<td>2121 (17.6)</td>
</tr>
<tr>
<td>Other hospital</td>
<td>682 (17.7)</td>
</tr>
<tr>
<td><strong>ICU length of stay (median, IQR)</strong></td>
<td>2.0, 3.0</td>
</tr>
<tr>
<td><strong>ICU mortality</strong></td>
<td>126 (3.3)</td>
</tr>
</tbody>
</table>

ICU: intensive care unit; IQR: interquartile range

On the day of admission, over 90% of patients (n=3 843) had at least one creatinine value available (Figure 4.2); the percentage then decreases to approximately 80%. A similar trend is seen when we consider the number of patients in the ICU who have their urine output documented each day (Figure 4.3). It should be noted that the standard of care in the ICU of The Hospital for Sick Children is hourly documentation of vital signs (e.g. heart rate, respiratory rate, blood pressure, etc.). Creatinine is monitored on a daily basis, more frequently if there are clinical implications. For patients with indwelling urinary catheters, urine output is documented hourly. The standard of care is to remove the catheter as soon as possible; however, once the catheter is removed, urine output is still documented with each void.
Figure 4.2: Number and proportion of patients with at least one serum creatinine value available by day (for the first 14 days of their ICU stay)

We assessed the proportion of patients who had at least one serum creatinine measurement during each day (based on 24 hour intervals from the time of ICU admission). During the first 24 hours of admission, 90% of patients had at least one creatinine measurement. This percentage dropped to just under 50% and then increased to 80% as the length of stay increased.
Figure 4.3: Number and proportion of patients with at least one urine output measurement available by day (for the first 14 days of their ICU stay)

We assessed the proportion of patients who had at least one urine output measurement during each day (based on 24 hour intervals from the time of ICU admission). During the first 24 hours of admission, over 95% of patients had at least one urine output measurement. This percentage dropped to just approximately 55% and then increased to roughly 90% as the length of stay increased.

The timing of the baseline creatinine measurements in the study population were as follows: 90.1% of baseline values are defined as the patient’s first creatinine measured within 24 hours of ICU admission; 5.7% were based on the most recent creatinine available within 3 months prior to the ICU admission; 4.2% had neither measure available and thus had an age- and sex-adjusted creatinine measure imputed for a baseline value. Of the 221 patients whose baseline is defined as the most recent pre-ICU creatinine, roughly 60% of these measurements are taken on the same day or the day prior to their admission to the ICU (Figure 4.4). Thus, based on the timing of measurements, it is likely that the pre-ICU
A creatinine value would estimate a creatinine measured within the first 24 hours of ICU admission.

![Figure 4.4: Timing of the most recent creatinine measurement available within 3 months prior to ICU admission for patients without a creatinine available during the first 24 hours of ICU admission (n=221)](image)

For patients who did not have a creatinine measure available within the first 24 hours of ICU admission, their baseline creatinine measure was the most recent value within three months of ICU admission. We assessed how recent these values were and found that over 40% had a measure taken on the same day of ICU admission (far right bar). Approximately 60% of patients had a measurement taken on the day of or the day prior to ICU admission.

For the majority of patients (90.1%) whose baseline creatinine measurement is defined as the first serum creatinine measured during the first 24 hours of their admission to the ICU, it is plausible that this value could be extremely high. A high baseline measure would make it highly unlikely to see an increase of 1.5 to meet the RIFLE-based definition of AKI. Despite
the skewness of the distribution of first creatinine measurements (by age group, Figures 4.5 through 4.7), only 93 of the 3,483 patients with a measurement available (2.7%) have an abnormally high creatinine measurement, based on the PELOD criteria (<1 year, ≥55µmol/L; 1-12 years, ≥100µmol/L; ≥12 years, ≥140µmol/L) (Leteurtre et al., 1999; Leteurtre et al., 2003).

Figure 4.5: Histogram of first creatinine measurement values within 24 hours of admission for patients under 1 year of age (n=1020)

For patients under 1 year of age, the distribution of first creatinine measures is highly skewed. However, few are above the PELOD criteria (≥55µmol/L) defining an abnormally high value.
Figure 4.6: Histogram of first creatinine measurement values within 24 hours of admission for patients between 1 and 12 years of age (n=1605)

For patients between 1 and 12 years of age, the distribution of first creatinine measures is highly skewed. However, few are above the PELOD criteria (≥100µmol/L) defining an abnormally high value.
Figure 4.7: Histogram of first creatinine measurement values within 24 hours of admission for patients 12 years of age and older (n=857)

For patients over 12 years of age, the distribution of first creatinine measures is highly skewed. However, few are above the PELOD criteria (≥140µmol/L) defining an abnormally high value.

Nine hundred and fifteen patients (23.7%) developed AKI at a median of 28 hours (IQR=43.0) after ICU admission. The severity of the first occurrence of AKI was: 84.8% ‘Risk’, 13.2% ‘Injury’ and 2.0% ‘Failure’. Sixty-six percent of patients with AKI achieved a maximum severity of ‘Risk’, 27.5% ‘Injury’ and 6.4% ‘Failure’. Patients who developed AKI had a longer length of stay in the ICU (median 5 days, IQR=8 versus 1 day, IQR=1) and significantly higher mortality (7.2%, 95% confidence interval (CI): 5.6%-9.1% versus 2.0%, 1.6%-2.6%) than those who did not develop AKI.

As previously stated, 90% of patients in the cohort had a baseline serum creatinine measurement available within the first 24 hours of ICU admission, 5.7% had a measure
available within 3 months prior to ICU admission and 4.2% had an imputed baseline value. To determine the effect of different baseline creatinine values on the estimated incidence of AKI, the RIFLE-GFR criteria were recalculated using the following estimates of baseline renal function:

1. The first serum creatinine measured within 24 hours of the patient’s admission to the ICU, available for 3,483 patients;

2. The most recent serum creatinine measured 3 months prior to the patient’s ICU admission, available for 2,633 patients;

3. An age- and sex-adjusted normal value (hereafter referred to as the imputation method), available for all 3,865 patients.

For the purposes of this comparison, only the GFR criteria were used to estimate the incidence of AKI. The imputation method resulted in the highest number of AKI cases (773 patients, 20.0%) whereas use of the most recent creatinine within 3 months of ICU admission resulted in an incidence of 16.3% (n=429). Use of the first creatinine within 24 hours of ICU admission resulted in the lowest incidence (7.0%, n=245). The associated severity levels are shown in Figure 4.8. However, when both the GFR and urine output criteria were used, we found no significant differences in estimated AKI incidence when comparing the three methods of assessing baseline renal function (Table 4.3).
When three different methods of estimation for baseline serum creatinine is compared, we see that the
imputation method (age- and gender-adjusted norms) results in the highest estimated incidence of
AKI whereas using the first serum creatinine within 24 hours of ICU admission results in the lowest
estimated incidence. Severity of AKI also varies across estimation methods, with the highest
proportion of the highest severity level, ‘Failure’, results from the imputation method.

<table>
<thead>
<tr>
<th>Baseline measurement</th>
<th>Estimated AKI incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>First SCr within 24h of ICU admission</td>
<td>23.2%</td>
</tr>
<tr>
<td>Most recent SCr within 3 months of ICU admission</td>
<td>28.1%</td>
</tr>
<tr>
<td>Age- and gender-adjusted norm</td>
<td>28.6%</td>
</tr>
</tbody>
</table>

SCr: serum creatinine

In the 2 412 patients (62.4%) that had both a creatinine measured within the first 24 hours of
their ICU admission and a creatinine measured within the 3 month period prior to their ICU
admission, the AKI severity classifications resulting from the use of each baseline measure
had an agreement of 89.2% and a weighted kappa of 0.58 (95% CI: 0.54 – 0.62), indicating moderate agreement (Cohen, 1968). The raw agreement increased to 92.4% when we dichotomized the RIFLE severity to a measure of AKI versus no AKI (kappa 0.67; 95% CI: 0.65 – 0.73), indicating substantial agreement between the estimated incidence of AKI according to the two baseline methods.

The RIFLE criteria have two components (GFR and urine output); both are intended to be used when assessing the severity of acute kidney injury. However, many studies use only the GFR criteria when defining AKI (M. B. Slater et al., 2012). In our patient cohort, 17.9% of patients met both the GFR and urine output criteria, 59.8% met only the urine output criteria, and 22.3% only met the GFR criteria at any point during their ICU stay. Translating this to estimates of AKI incidence, when we considered only the GFR criteria to define AKI, 368 patients (9.5% of the study cohort) had a RIFLE severity of ‘Risk’ or higher. If we solely consider the urine output criteria, 711 patients (18.4%) had AKI (Figure 4.9).
Figure 4.9: Estimated incidence of AKI based on varying RIFLE criteria components

When comparing the estimated incidence of AKI using different components of the RIFLE criteria, we find that using only the GFR criteria (i.e. relative changes in serum creatinine) results in the lowest estimate of AKI (9.5%). Using only the urine output criteria, the estimated incidence of AKI increases to 18.4%. Using both criteria, the incidence of AKI in the study population is estimated to be 23.7%.

AKI: acute kidney injury; GFR: glomerular filtration rate

Unadjusted analyses revealed that the development of AKI was associated with younger age, unplanned ICU admissions, cardiac surgical or medical ICU admissions, International Classification of Disease (ICD) admission diagnosis codes of circulatory disorders, endocrine disorders, infectious disease, neoplasms, and respiratory disorders, and receiving one or more nephrotoxic medications prior to ICU admission (Table 4.4). During their ICU care, patients who experienced sepsis, shock, septic shock or organ dysfunction or received intravenous radiologic contrast, mechanical ventilation, extracorporeal membrane oxygenation (ECMO)
or one or more nephrotoxic medications were significantly more likely to develop AKI (Table 4.4).

Twenty-four risk factors were eligible for multivariable analyses; 4 were excluded due to high degrees of collinearity (i.e. mechanical ventilation, SIRS, shock and septic shock). After adjustment in a multivariable logistic regression model, we identified 12 variables for our final model using backward stepwise regression (Table 4.5). Increasing age (OR=1.02, 95% CI: 1.00-1.03), unplanned admission to the ICU (OR=1.88, 95% CI: 1.38-2.56), admission diagnoses of circulatory (OR=1.46, 95% CI: 1.09-1.95) or respiratory system disorders (OR=1.43, 95% CI: 1.10-1.88), increasing Pediatric Risk of Mortality (PRISM) score (OR=1.03, 95% CI: 1.02-1.05), in-ICU respiratory dysfunction (OR=2.90, 95% CI: 2.29-3.67), use of ECMO (OR=2.72, 95% CI: 1.14-6.52) and administration of nephrotoxic medication(s) both prior to (OR=1.43, 95% CI: 1.12-1.84) and during the ICU admission (OR=3.37, 95% CI: 2.66-4.28) increased the odds of developing AKI. Non-cardiac surgical admissions (OR=0.69, 95% CI: 0.50-0.95), use of intravenous radiologic contrast (OR=0.76, 95% CI: 0.59-0.97), and in-ICU neurologic dysfunction (OR=0.62, 95% CI: 0.51-0.76) were associated with a reduced occurrence of AKI. Cardiac surgical admissions had an increased odds of developing AKI (OR=1.26, 95% CI: 0.88-1.81) compared with non-surgical admissions, however this result was not statistically significant.
Table 4.4: Risk factors for developing acute kidney injury (bivariate analyses); n(%) unless specified otherwise

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>AKI (n=915)</th>
<th>No AKI (n=2 950)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At ICU admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission age in years (median, IQR)</td>
<td>2.9, 11.1</td>
<td>4.8, 11.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>381 (41.6)</td>
<td>1 320 (44.8)</td>
<td>0.0982</td>
</tr>
<tr>
<td>Unplanned ICU admission</td>
<td>553 (60.4)</td>
<td>1 334 (45.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical, cardiac</td>
<td>318 (34.8)</td>
<td>706 (23.9)</td>
<td></td>
</tr>
<tr>
<td>Surgical, non-cardiac</td>
<td>101 (11.0)</td>
<td>996 (33.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical</td>
<td>496 (54.2)</td>
<td>1 248 (42.3)</td>
<td></td>
</tr>
<tr>
<td>Admission diagnoses (ICD-10 codes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory (I00-I99)</td>
<td>99 (10.8)</td>
<td>188 (6.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Endocrine (E00-E99)</td>
<td>13 (1.4)</td>
<td>124 (4.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infectious disease (A00-B99)</td>
<td>36 (3.9)</td>
<td>58 (1.8)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Injury (S00-T98)</td>
<td>71 (7.8)</td>
<td>210 (7.1)</td>
<td>0.5142</td>
</tr>
<tr>
<td>Neoplasms (C00-D48)</td>
<td>29 (3.2)</td>
<td>246 (8.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nervous system (G00-G99)</td>
<td>70 (7.7)</td>
<td>224 (7.6)</td>
<td>0.9546</td>
</tr>
<tr>
<td>Respiratory (J00-J99)</td>
<td>122 (13.3)</td>
<td>242 (8.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PRISM(^a) score (median, IQR)</td>
<td>5.0, 7.0</td>
<td>3.0, 6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nephrotoxic medication administration prior to ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>149 (16.3)</td>
<td>264 (8.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>544 (59.5)</td>
<td>2 226 (75.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown</td>
<td>222 (24.3)</td>
<td>460 (15.6)</td>
<td></td>
</tr>
<tr>
<td><strong>During ICU admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIRS</td>
<td>649 (70.9)</td>
<td>2 007 (68.0)</td>
<td>0.0989</td>
</tr>
<tr>
<td>Sepsis</td>
<td>108 (11.8)</td>
<td>221 (7.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shock</td>
<td>672 (73.4)</td>
<td>1 709 (57.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septic shock</td>
<td>89 (9.7)</td>
<td>188 (6.4)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Cardiovascular organ dysfunction</td>
<td>701 (76.6)</td>
<td>1 779 (60.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neurologic organ dysfunction</td>
<td>657 (71.8)</td>
<td>1 969 (66.8)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Haematologic organ dysfunction</td>
<td>144 (15.7)</td>
<td>265 (9.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatic organ dysfunction</td>
<td>394 (43.1)</td>
<td>938 (31.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiratory organ dysfunction</td>
<td>732 (80.0)</td>
<td>1 462 (49.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intravenous radiologic contrast</td>
<td>132 (14.4)</td>
<td>346 (11.7)</td>
<td>0.0304</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>729 (79.7)</td>
<td>1 451 (49.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECMO</td>
<td>20 (2.2)</td>
<td>8 (0.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nephrotoxic medication administration</td>
<td>802 (87.7)</td>
<td>1 613 (54.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; ICD: International Classification of Disease; ICU: intensive care unit; IQR: interquartile range; PRISM: Pediatric Risk of Mortality; SIRS: systemic inflammatory response syndrome

\(^a\) PRISM score ranges from 0 to 48, with a higher score indicating more severe illness
Table 4.5: Risk factors of acute kidney injury in critically ill children (multivariable analysis)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted OR\textsuperscript{a}</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At ICU admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission age (per 1 year increase in age)</td>
<td>1.02</td>
<td>1.00 – 1.03</td>
</tr>
<tr>
<td>Unplanned ICU admission</td>
<td>1.88</td>
<td>1.38 – 2.56</td>
</tr>
<tr>
<td>Admission type (ref: medical admission)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical, cardiac</td>
<td>1.26</td>
<td>0.88 – 1.81</td>
</tr>
<tr>
<td>Surgical, non-cardiac</td>
<td>0.69</td>
<td>0.50 – 0.95</td>
</tr>
<tr>
<td>Circulatory admission diagnosis</td>
<td>1.46</td>
<td>1.09 – 1.95</td>
</tr>
<tr>
<td>Respiratory admission diagnosis</td>
<td>1.43</td>
<td>1.10 – 1.88</td>
</tr>
<tr>
<td>PRISM score (per 1 unit increase in score)</td>
<td>1.03</td>
<td>1.02 – 1.05</td>
</tr>
<tr>
<td>Nephrotoxic medication administration prior to ICU admission (ref: no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.43</td>
<td>1.12 – 1.84</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.22</td>
<td>0.96 – 1.55</td>
</tr>
<tr>
<td><strong>During ICU admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological organ dysfunction</td>
<td>0.62</td>
<td>0.51 – 0.76</td>
</tr>
<tr>
<td>Respiratory organ dysfunction</td>
<td>2.90</td>
<td>2.29 – 3.67</td>
</tr>
<tr>
<td>Intravenous radiologic contrast</td>
<td>0.76</td>
<td>0.59 – 0.97</td>
</tr>
<tr>
<td>ECMO</td>
<td>2.72</td>
<td>1.14 – 6.52</td>
</tr>
<tr>
<td>Nephrotoxic medication administration</td>
<td>3.37</td>
<td>2.66 – 4.28</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; PRISM: Pediatric Risk of Mortality
\textsuperscript{a} OR adjusted for all 12 risk factors included in the multivariable model; Hosmer and Lemeshow goodness-of-fit test: $\chi^2=5.6391$, $p=0.6876$

### 4.5 Discussion

We evaluated the incidence and risk factors for acute kidney injury using an accepted classification system (Bellomo et al., 2004) in a cohort of 3,865 critically ill children admitted to a large, academic intensive care unit over a 42-month period. To our knowledge, this is the largest study of AKI in critically ill children performed to date. We have also demonstrated the feasibility of using electronic data to assess AKI utilizing the RIFLE criteria.
We found that AKI occurred in nearly one-quarter of all critically ill children. Previous studies of RIFLE-defined AKI report rates varying from 10% to 83% (M. B. Slater et al., 2012); no studies were found that applied the full RIFLE criteria in a similar patient population. Two previous studies in a similar patient population did not evaluate urine output (Bailey et al., 2007; Schneider et al., 2010) and one used a study-specific definition of AKI (the doubling of serum creatinine relative to the creatinine level at ICU admission or relative to the upper limit of normal for age and sex) (Bailey et al., 2007), limiting comparison to this study. Our results reinforce the clinical relevance of AKI in this population as AKI was associated with an increased ICU length of stay of 4 days and children with AKI had a mortality rate roughly 3.5 times that of children without AKI. The increased mortality rate seen in critically ill children with AKI adds to the growing evidence that the development of AKI itself contributes to increased mortality, rather than the previous belief that patients with AKI die because of their underlying disease (E.A.J. Hoste & De Corte, 2011).

Increased risk of AKI was seen with increasing age, ICU admission diagnoses of circulatory or respiratory disorders, increasing PRISM score, administration of nephrotoxic medication(s) prior to ICU admission, in-ICU respiratory dysfunction, use of ECMO and administration of nephrotoxic medication(s) during the ICU stay, consistent with previous work (Akcan-Arikan et al., 2007; Bailey et al., 2007; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; Palmieri et al., 2009; F. B. Plotz et al., 2005; Schneider et al., 2010). While trauma has been previously reported as a risk factor of AKI in both adults (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; Shigehiko Uchino et al., 2006) and children (Wohlauer et al., 2012), our findings correspond to those of Bailey et al (Bailey et al., 2007) and Plotz et al (F. B. Plotz et al., 2005) who also found the association between AKI and an
admission diagnosis of trauma to be statistically non-significant in critically ill children. Our finding that radiologic contrast administration was associated with lower rates of AKI was surprising (Brasch, 2008; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; Seeliger, Sendeski, Rihal, & Persson, 2012; Waybill & Waybill, 2001); however, the association between contrast administration and AKI has recently been questioned. A recent meta-analysis of observational studies revealed that the risk of AKI, death and dialysis in patients receiving contrast medium was similar to those who did not (McDonald et al., 2013). Perhaps contrast use is a marker of relative health as, according to clinical guidelines (Benko et al., 2007; Solomon & Deray, 2006; Stacul et al., 2011), contrast is withheld in patients perceived to be at risk for AKI. However, patients in our cohort who received intravenous contrast did not appear to be healthier than their peers; they were significantly more likely to have unplanned admissions to the ICU, have higher illness severity scores (PRISM), longer lengths of stay and higher mortality rates (data not shown). The perception of risk of kidney damage with contrast administration may be influential here; increased hydration is recommended to minimize the deleterious effects on the kidney (Benko et al., 2007; Solomon & Deray, 2006; Stacul et al., 2011) and patients are closely monitored for signs of kidney injury. Our findings may be explained by timing: serum creatinine levels have been shown to peak three days after contrast administration (Marenzi et al., 2004; Solomon, 1998) and the effects of contrast use may not be apparent until after ICU discharge. Further work is needed to elucidate the causal association between contrast administration and the development of acute kidney injury in critically ill children.

Of the twelve independent risk factors identified, seven were evident prior to ICU admission while five occurred during the ICU stay. All in-ICU risk factors are markers of disease severity (organ dysfunction) or therapeutic intervention (intravenous contrast, ECMO,
nephrotoxic medication). The single greatest risk factor of in-ICU AKI was the administration of nephrotoxic medications, indicating that scrutiny of the drugs used in the paediatric ICU setting is warranted. Lessons from contrast guidelines (Benko et al., 2007; Solomon & Deray, 2006; Stacul et al., 2011) and recent recommendations for aminoglycoside and amphotericin-induced AKI prevention (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) should be applied to all potential nephrotoxic drugs: nephrotoxic medications should be avoided wherever possible for all patients, especially those identified to be in high-risk populations, such those urgently admitted to ICU, those who develop respiratory dysfunction, and those treated with ECMO. Further research into the risks of specific drugs on the renal system is warranted to better understand opportunities for ‘nephroprotection’ as are investigations of the clinical outcomes of associated with use of potentially less nephrotoxic alternative therapies.

4.5.1 Limitations

Our study has several limitations. First, while the use of electronic data allowed study of a large patient population, it limited some of the data elements for use in analysis. Some important clinical variables of interest, such as cardiac arrest or duration of cardiac bypass, were not available in our electronic systems. This data availability also affected our definition of AKI; while a pediatric modification of the RIFLE exists (pRIFLE) (Akcan-Arikan et al., 2007), it requires the calculation of estimated creatinine clearance. Unfortunately, patient height is not captured in our electronic data sources and, as such, we were unable to calculate creatinine clearance. In addition, our electronic sources did not include medication reconciliation from other institutions and we did not have other access to medical records from other institutions. Accordingly, we were only able to assess nephrotoxic drug exposure
during the same hospital admission prior to admission to the ICU; medications administered in other hospitals or at home could not be captured. The definition of nephrotoxic medications used in our analysis was based on adverse reactions noted in drug monographs and in consultation with clinical experts; however, we may have excluded potentially relevant medications. In addition, the use of a binary measure of medication exposure may have oversimplified the association between drug exposure and nephrotoxicity.

Finally, some of the clinical data we were interested in were highly correlated and definitions of many risk factors of interest were similar (e.g., Systemic Inflammatory Response Syndrome (SIRS) and sepsis, shock and cardiovascular dysfunction, mechanical ventilation and respiratory dysfunction). While addressing collinearity issues and excluding variables from the multivariable model strengthens our analysis, the choices made may limit comparability to other research. For example, while we chose to include respiratory dysfunction over mechanical ventilation, or cardiovascular organ dysfunction over shock, others may have made the opposite decisions.

Despite these limitations, we have demonstrated the feasibility of the use of electronic health data to evaluate detailed patient level outcomes, such as the utilization of both changes in serum creatinine and urine output to define AKI using the RIFLE criteria.

4.6 Conclusions

This evaluation of a large cohort of critically ill children found AKI to be a common event in the paediatric ICU, with complex and multifactorial origins. Seven risk factors associated
with the development of AKI were pre-existing at ICU admission while five occurred during the patient’s ICU care. The single greatest risk factor for AKI was the administration of nephrotoxic medications during the ICU stay. The identification of risk factors suggests that prospective AKI risk assessment may be possible and allow for targeted interventions to reduce AKI and improve the outcomes of critically ill children.
Chapter 5  Acute Kidney Injury and Exposure to Nephrotoxic Medications in Critically Ill Children: A Nested Case-Control Study
5.1 Overview

The overall goal of this work was to evaluate the contributions of drug therapy to acute kidney injury (AKI). The previous chapter presented a cohort study that evaluated the characteristics and clinical factors that place paediatric patients at higher risk for developing AKI during treatment in the ICU. We found several risk factors associated with the development of AKI, some pre-existing at ICU admission while others occurred during the patient’s ICU care. However, the single greatest risk factor for AKI was the administration of one or more nephrotoxic medication during the ICU stay.

Accordingly, the next step of the thesis work is to evaluate the association between specific nephrotoxic medications and the development of AKI, while controlling for underlying differences in risk. In order to accomplish this, we performed a nested case-control study, the results of which are presented in this chapter. Critically ill children who developed AKI during their ICU admission were matched to patients who did not develop AKI. Exposure to nephrotoxic medications was compared between the two patient groups. The analysis was adjusted for underlying differences in risk factors of AKI based on the cohort analysis previously presented (Chapter 4).

5.2 Introduction

The incidence of acute kidney injury (AKI) in hospitalized children ranges from 9% to 83% (Hassinger et al., 2012; P. Mehta et al., 2012; Morgan et al., 2013; M. B. Slater et al., 2012; Toth et al., 2012) and critically ill children are at particular risk of developing AKI (Kidney
Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). Children who develop AKI have poor outcomes, including increased morbidity and mortality (D. J. Askenazi et al., 2006; D. J. Askenazi et al., 2009; Hui-Stickle et al., 2005). A number of factors increase a patient’s risk for developing AKI, such as critical illness, sepsis, circulatory shock and trauma (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). While some factors, such as age and gender (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012), are non-modifiable, others, including exposure to nephrotoxic medications, are under the control of the prescriber and present a potential opportunity to decrease the risk of AKI.

Exposure to nephrotoxic medications is the second most common cause of AKI, estimated to account for 16% of pediatric AKI (Hui-Stickle et al., 2005). However, there is lack of pediatric data available regarding the actual incidence of nephrotoxicity for many medications known to have deleterious effects on the kidneys. Moffet and Goldstein recently assessed the association between nephrotoxic medications and the risk of developing AKI in hospitalized, non-critically ill pediatric patients (Moffett & Goldstein, 2011); however, the risk of nephrotoxic medication-induced AKI in critically ill children remains unknown.

The objective of this study was to determine the risk of developing AKI after the initiation of nephrotoxic medication within the intensive care unit (ICU) setting among critically ill children.
5.3 Methods

We performed a nested case-control study in a cohort of critically ill children at The Hospital for Sick Children in Toronto, Ontario, Canada. The cohort that was used in the previous study regarding risk factors of AKI (Chapter 4) was the basis for the nested case-control study. As stated in the previous chapter, children who were admitted to the ICU between January 2006 and June 2009 were eligible for the cohort and were followed for the duration of their ICU stay. Patients with an admission diagnosis of renal disease (known primary renal failure, post-renal transplant, or chronic renal failure), drug overdose, tumor lysis syndrome, haemolytic uraemic syndrome (conditions with known renal complications) or methylmalonic acidemia or urea cycle defect (metabolic conditions treated with dialysis) were excluded. In addition, we excluded patients who were less than two weeks of age to minimize the impact of maternal creatinine on measured creatinine levels in the child (Guignard & Drukker, 1999; Miall et al., 1999) and those who were admitted to the ICU for less than six hours as these patients tend to be admitted for observation or minor procedures only. Patients with no creatinine or urine output measurements during their ICU admission were also excluded as they were missing necessary measurements to assess renal function. Only the first ICU admission for each patient was considered; repeat admissions during the study period were not included.

5.3.1 Case Definition

Cases were classified as having AKI according to the RIFLE (Bellomo et al., 2004) criteria: a RIFLE severity of ‘Risk’ or higher (a 1.5 increase in serum creatinine from baseline or a urine output of <0.5ml/kg/hour for 6 hours) defined a patient as having AKI. To assess AKI
occurring due to exposures specifically within the ICU environment, the baseline creatinine measure was slightly modified from the RIFLE and defined as the first serum creatinine measurement within 24 hours of ICU admission. If this creatinine measure was unavailable, consistent with the RIFLE (Bellomo et al., 2004) criteria the most recent creatinine measurement within 3 months prior to ICU admission was used; otherwise the mean age- and gender-adjusted norm (Schwartz, Haycock, & Spitzer, 1976) was used. The date and time of the first diagnosis of AKI was defined as the index date for each case.

5.3.2 Identification of Controls

Incidence density sampling (Szklo, 2006) was used to identify control patients for each case patient. Using this sampling methodology, controls were selected from a random sample of the patients remaining in the cohort at the time each case occurs (the index date), equivalent to matching cases and controls on follow-up time (Szklo, 2006) (Figure 5.1). As we were concerned about controlling for exposure to nephrotoxic medications prior to ICU admission, controls were matched 1:1 to cases on the basis of exposure to nephrotoxic medications during the hospitalization directly prior to admission to the ICU. Prior nephrotoxic drug administration was classified according to three categories: yes, no or unknown. The ‘unknown’ classification indicated that the patient was admitted directly to the ICU from another hospital. This reflected the fact that we were unable to assess medications administered in other hospitals or at home and thus were only able to assess nephrotoxic drug exposure during the same hospital admission.
Figure 5.1: Incidence density sampling

At the time a patient is diagnosed with AKI and becomes a ‘case’, they are matched to a control. Controls are randomly selected from the patients still in the cohort at this time. Thus, a control can later become a case. This process essentially matches cases and controls on follow-up time. Modified from Szklo & Nieto. Epidemiology: Beyond the Basics. 2nd ed. p28 (Szklo, 2006)

5.3.3 Nephrotoxic Drug Exposure

The main exposure of interest for this study is the administration of nephrotoxic medications during the patient’s ICU stay. As previously discussed in Chapter 4, a list of potential nephrotoxic medications was compiled according to adverse event information contained in the drug monographs of the hospital formulary, the Compendium of Pharmaceutical and Specialties (Compendium of Pharmaceuticals and Specialties 2013, 2012) and the Pediatric Dosage Handbook (Taketomo et al., 2012). Using a Delphi process involving clinical
experts, including a paediatric intensivist, paediatric pharmacologist and paediatric pharmacists, the following 29 medications were considered to have relevant nephrotoxic effects: acyclovir, amikacin, amphotericin, captopril, carboplatin, cidofovir, cisplatinum, cyclophosphamide, cyclosporine, enalapril, enalaprilat, ethacrynic acid, flucytosine, foscarnet, furosemide, ganciclovir, gentamicin, hydrochlorothiazide, ibuprofen, ifosfamide, indomethacin, ketorolac, methotrexate, penicillin, ramipril, sirolimus, tacrolimus, tobramycin, and vancomycin. Further details of this process are outlined in Section 4.3.1.

During the patient’s ICU stay, the administration of each drug was captured as a binary variable (yes/no). All data were evaluated prior to the index date of the first diagnosis of AKI.

While the main interest of this study was exposure to nephrotoxic medications during the ICU stay, we wanted to control for previous exposures to nephrotoxic drugs. As such, exposure to any of the 29 nephrotoxic medications listed above during the hospitalization immediately before the ICU admission was captured for each patient in the cohort. Patients who were admitted directly to the ICU from another hospital were classified as having unknown prior nephrotoxic medication exposure. As previously stated, cases and controls were matched on their prior exposure. Analyses were stratified according to the administration of nephrotoxic drugs during the hospitalization prior to ICU admission as a means to control for differences in past exposures.

5.3.4 Covariates

Based on previous research (Chapter 4), the following known risk factors for AKI were abstracted: age; unplanned ICU admission; admission type (surgical, cardiac; surgical, non-
cardiac; medical); International Classification of Disease (ICD-10) (World Health Organization, 2010) admission diagnoses of circulatory or respiratory disorders, Pediatric Risk of Mortality (PRISM) score (Pollack et al., 1988); in-ICU neurological or respiratory dysfunction, defined as a Pediatric Logistic Organ Dysfunction (PELOD) (Leteurtre et al., 1999) score of one or greater for each system; administration of intravenous radiologic contrast; and the use of extracorporeal membrane oxygenation (ECMO). All data were evaluated prior to date of the first diagnosis of AKI (the index date).

5.3.5 Data Analysis

Descriptive statistics were used to characterize the demographic and clinical composition of the cases and controls. Conditional logistic regression was used to estimate the association between individual nephrotoxic medications and AKI. Medications with a bivariate significance level of 0.2 or less were included in a multivariable conditional logistic regression model. Drugs with no independent association at the bivariate level were grouped into a single binary variable (‘other nephrotoxic medications’) in order to control for the potential additive effect of drug exposure. To adjust for underlying differences in AKI risk, this model included risk factors of AKI found to be statistically significant (p<0.05) in bivariate analyses. Finally, stratified multivariable models based on prior nephrotoxic medication exposure were also conducted. All analysis was performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). Small sample sizes (<5) were suppressed for publication purposes.

This study received approval from The Hospital for Sick Children’s Research Ethics Board.
5.4 Results

A total of 6,326 admissions to the ICU were identified during the study period. Of these, 3,865 patients were eligible for the cohort and 915 (23.7%) were categorized as having AKI.

Nine hundred and fourteen case-control pairs were identified and these patients constitute the study sample that was evaluated.

Forty-one percent of the study sample was over 6 years of age and 43% were female (Table 5.1). Cases and controls were matched 1:1 according to previous exposure to nephrotoxic drugs: 16.2% (n=148) of case-control pairs were exposed to a nephrotoxic medication during their hospitalization prior to the ICU admission; the previous exposure status of 24.3% (n=222) was unknown as they were transferred directly to the ICU from another hospital.

This process identified 914 case-control pairs, with one case unable to be matched a control. The median observation time, from time of ICU admission to the onset of AKI (the index date), of the case-control pairs was 28 hours (IQR=43 hours).
Table 5.1: Demographics and clinical composition of case and control patients; n(%) unless specified otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=1828)</th>
<th>Cases (n=914)</th>
<th>Controls (n=914)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term neonate (≤27 days)</td>
<td>51 (2.8)</td>
<td>28 (3.1)</td>
<td>23 (2.5)</td>
</tr>
<tr>
<td>Infant (28 days – 12 months)</td>
<td>670 (36.7)</td>
<td>330 (36.1)</td>
<td>340 (37.2)</td>
</tr>
<tr>
<td>Toddler (13 months – 2 years)</td>
<td>156 (8.5)</td>
<td>71 (7.8)</td>
<td>85 (9.3)</td>
</tr>
<tr>
<td>Early childhood (2 – 5 years)</td>
<td>210 (11.5)</td>
<td>100 (10.9)</td>
<td>110 (12.0)</td>
</tr>
<tr>
<td>Middle childhood (6 – 11 years)</td>
<td>307 (16.8)</td>
<td>141 (15.4)</td>
<td>166 (18.2)</td>
</tr>
<tr>
<td>Early adolescence (12 – 18 years)</td>
<td>434 (23.7)</td>
<td>244 (26.7)</td>
<td>190 (20.8)</td>
</tr>
<tr>
<td><strong>Sex [Female]</strong></td>
<td>778 (42.6)</td>
<td>380 (41.6)</td>
<td>398 (43.5)</td>
</tr>
<tr>
<td>Nephrotoxic medication exposure prior to ICU admission(a,b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>296 (16.2)</td>
<td>148 (16.2)</td>
<td>148 (16.2)</td>
</tr>
<tr>
<td>No</td>
<td>1088 (59.5)</td>
<td>544 (59.5)</td>
<td>544 (59.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>444 (24.3)</td>
<td>222 (24.3)</td>
<td>222 (24.3)</td>
</tr>
<tr>
<td>Unplanned admission</td>
<td>1131 (61.8)</td>
<td>552 (60.4)</td>
<td>579 (63.4)</td>
</tr>
<tr>
<td><strong>Admission type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical, cardiac</td>
<td>536 (29.3)</td>
<td>318 (34.8)</td>
<td>218 (23.9)</td>
</tr>
<tr>
<td>Surgical, non-cardiac</td>
<td>259 (14.2)</td>
<td>101 (11.0)</td>
<td>158 (17.3)</td>
</tr>
<tr>
<td>Medical</td>
<td>1033 (56.5)</td>
<td>495 (54.2)</td>
<td>538 (58.9)</td>
</tr>
<tr>
<td>Circulatory admission diagnosis</td>
<td>170 (9.3)</td>
<td>96 (10.7)</td>
<td>72 (7.9)</td>
</tr>
<tr>
<td>Respiratory admission diagnosis</td>
<td>228 (12.5)</td>
<td>122 (13.4)</td>
<td>106 (11.6)</td>
</tr>
<tr>
<td>PRISM score (median, IQR)</td>
<td>5.0, 7.0</td>
<td>5.0, 7.0</td>
<td>5.0, 7.0</td>
</tr>
<tr>
<td>In-ICU neurologic organ dysfunction</td>
<td>1367 (74.9)</td>
<td>656 (71.8)</td>
<td>711 (77.8)</td>
</tr>
<tr>
<td>In-ICU respiratory organ dysfunction</td>
<td>1365 (74.7)</td>
<td>731 (80.0)</td>
<td>634 (69.4)</td>
</tr>
<tr>
<td>Intravenous radiologic contrast</td>
<td>337 (18.4)</td>
<td>131 (14.3)</td>
<td>206 (22.5)</td>
</tr>
<tr>
<td>ECMO</td>
<td>36 (2.0)</td>
<td>20 (2.2)</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>In-ICU administration of nephrotoxic medication(b)</td>
<td>1474 (80.6)</td>
<td>801 (87.6)</td>
<td>673 (73.6)</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range; PRISM: Pediatric Risk of Mortality

\(a\) Equal distribution between cases and controls due to matching strategy

\(b\) Nephrotoxic medication defined as administration of any of the following: acyclovir, amikacin, amphotericin, captopril, carboplatin, cidofovir, cisplatinum, cyclophosphamide, cyclosporine, enalapril, enalaprilat, ethacrynic acid, flu cytosine, foscarcet, furosemide, ganciclovir, gentamicin, hydrochlorothiazide, ibuprofen, ifosfamide, indomethacin, ketorolac, methotrexate, penicillin, ramipril, sirolimus, tacrolimus, tobramycin, and vancomycin
When comparing known risk factors for AKI, cases were more likely to be admitted to the ICU post cardiac surgery (OR=1.73, 95% CI: 1.34-2.22), admitted with an ICD-10 admission diagnosis of circulatory system disease (OR=1.39, 95% CI: 1.02-1.91) and develop respiratory dysfunction while in the ICU (OR=1.81, 95% CI: 1.45-2.26) than their matched controls. Cases were also less likely to develop in-ICU neurological dysfunction (OR=0.72, 95% CI: 0.58-0.89) or receive intravenous radiologic contrast (OR=0.56, 95% CI: 0.43-0.72).

Eighty percent of the study sample was exposed to one or more nephrotoxic medication during the observation period, with a median of 2 nephrotoxic medications (minimum=0, maximum=8). Furosemide (administered to 67.8% of patients), vancomycin (28.7%) and gentamicin (21.4%) were the most frequently administered nephrotoxic medications while cidofovir (0.2%), enalaprilat (0.2%), foscarinet (0.2%), carboplatin (0.1%), indomethacin (0.1%), methotrexate (0.1%), ramipril (0.1%) and sirolimus (0.1%) were rarely used. Cisplatinum, fluctosine and ifosfamide were not administered to any patient during the observation period.

Cases were significantly more likely than controls to have been exposed to at least one nephrotoxic medication (OR=2.60, 95% confidence interval (CI): 2.01-3.37). Exposure to additional nephrotoxic medications increased the risk of AKI by 30% for each additional drug (OR=1.30, 95% CI: 1.21-1.40). Compared to their matched control, cases were more likely to have been administered one or more of the following nephrotoxic medications prior to developing AKI (Table 5.2): the immunosuppressants, cyclosporine (OR=3.0, 95% CI: 1.28-7.06) and tacrolimus (OR=2.06, 95% CI: 1.17-3.61); antibiotics, gentamicin (OR=1.84, 95% CI: 1.44-2.35) and vancomycin (OR=1.29, 95% CI: 1.04-1.59); captopril, an angiotensin-converting enzyme (ACE) inhibitor (OR=1.74, 95% CI: 1.15-2.64); furosemide,
a diuretic (OR=2.23, 95% CI: 1.80 -2.76); ganciclovir, an antiviral (OR=2.93, 95% CI: 1.63-5.27); and ketorolac, a non-steroidal anti-inflammatory (NSAID) (OR=1.62, 95% CI: 1.18-2.25).

Table 5.2: Medication exposure during ICU treatment for case and control patients for all identified nephrotoxic drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cases (n=914)</th>
<th>Controls (n=914)</th>
<th>OR(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>69 (7.6)</td>
<td>63 (6.9)</td>
<td>1.10 (0.77 – 1.57)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>10 (1.1)</td>
<td>9 (1.0)</td>
<td>1.11 (0.45 – 2.73)</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>30 (3.3)</td>
<td>23 (2.5)</td>
<td>1.33 (0.76 – 2.35)</td>
</tr>
<tr>
<td>Captopril</td>
<td>65 (7.1)</td>
<td>39 (4.3)</td>
<td>1.74 (1.15 – 2.64)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>0 (0.0)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>&lt;5 (&lt;0.5)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>1.00 (0.14 – 7.10)</td>
</tr>
<tr>
<td>Cisplatinum</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>6 (0.7)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>2.00 (0.5 – 8.0)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>21 (2.3)</td>
<td>7 (0.8)</td>
<td>3.00 (1.28 – 7.06)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>13 (1.4)</td>
<td>8 (0.9)</td>
<td>1.71 (0.68 – 4.35)</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>&lt;5 (&lt;0.5)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>0.50 (0.05 – 5.51)</td>
</tr>
<tr>
<td>Ethacyrnic acid</td>
<td>24 (2.6)</td>
<td>17 (1.9)</td>
<td>1.47 (0.76 – 2.83)</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Fosfamidene</td>
<td>0 (0.0)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>Furosemide</td>
<td>695 (76.1)</td>
<td>544 (59.5)</td>
<td>2.23 (1.80 – 2.76)</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>46 (5.0)</td>
<td>17 (1.9)</td>
<td>2.93 (1.63 – 5.27)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>238 (26.0)</td>
<td>154 (16.9)</td>
<td>1.84 (1.44 – 2.35)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>10 (1.1)</td>
<td>5 (0.6)</td>
<td>2.00 (0.68 – 5.85)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>137 (15.0)</td>
<td>114 (12.5)</td>
<td>1.25 (0.95 – 1.64)</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>&lt;5 (&lt;0.5)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>1.00 (0.06 – 16.00)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>109 (11.9)</td>
<td>72 (7.9)</td>
<td>1.62 (1.18 – 2.25)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>&lt;5 (&lt;0.5)</td>
<td>&lt;5 (&lt;0.5)</td>
<td>1.00 (0.06 – 16.00)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>15 (1.6)</td>
<td>19 (2.1)</td>
<td>0.78 (0.39 – 1.56)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>&lt;5 (&lt;0.5)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>&lt;5 (&lt;0.5)</td>
<td>0 (0.0)</td>
<td>n/a</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>37 (4.1)</td>
<td>18 (2.0)</td>
<td>2.06 (1.17 – 3.61)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>13 (1.4)</td>
<td>10 (1.1)</td>
<td>1.33 (0.56 – 3.16)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>284 (31.1)</td>
<td>240 (26.3)</td>
<td>1.29 (1.04 – 1.59)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for sampling and matching strategy
Nine nephrotoxic medications were included in a multivariable conditional logistic regression (Table 5.3). The remaining 20 medications, while having no independent association at the bivariate level, were grouped together to control for the potential additive effect of medication exposure. Administration of ganciclovir, furosemide, ketorolac or gentamicin increased the odds of developing AKI. Controlling for underlying differences in risk factors for AKI, only ganciclovir (adjusted OR=4.23, 95% CI: 1.54-11.58), furosemide (adjusted OR=1.88, 95% CI: 1.45-2.43), and gentamicin (adjusted OR=1.73, 95% CI: 1.32-2.29) remained statistically significant.

When the models were stratified according to previous nephrotoxic medication exposure, few differences were seen in the model results between patients who did and did not receive nephrotoxic medications during their hospitalization prior to ICU admission (Table 5.4).
Table 5.3: Conditional logistic regression model including all nephrotoxic medications
(OR, 95% CI)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adjusted model&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model further adjusted for risk factors&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>2.80 (1.13 – 6.95)</td>
<td>4.23 (1.54 – 11.58)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>1.99 (1.59 – 2.49)</td>
<td>1.88 (1.45 – 2.43)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1.67 (1.29 – 2.18)</td>
<td>1.73 (1.32 – 2.29)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>1.72 (1.22 – 2.42)</td>
<td>1.19 (0.79 – 1.78)</td>
</tr>
<tr>
<td>Captopril</td>
<td>1.48 (0.96 – 2.29)</td>
<td>1.36 (0.86 – 2.14)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.00 (0.78 – 5.14)</td>
<td>1.49 (0.55 – 4.03)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.95 (0.70 – 1.28)</td>
<td>0.86 (0.63 – 1.17)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.95 (0.40 – 2.27)</td>
<td>0.70 (0.27 – 1.80)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.14 (0.89 – 1.46)</td>
<td>1.18 (0.90 – 1.54)</td>
</tr>
<tr>
<td>Other nephrotoxic</td>
<td>1.11 (0.84 – 1.47)</td>
<td>1.17 (0.87 – 1.58)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for sampling and matching strategy
<sup>b</sup> Adjusted for: admission type, circulatory admission diagnosis, in-ICU neurological dysfunction, in-ICU respiratory dysfunction, intravenous radiologic contrast
<sup>c</sup> Includes: acyclovir, amikacin, amphotericin, carboplatin, cidofovir, cisplatinum, cyclosporine, enalapril, enalaprilat, ethacrynic acid, fluycytosine, foscarnet, hydrochlorothiazide, ifosfamide, indomethacin, methotrexate, penicillin, ramipril, sirolimus, tobramycin

Note: Adjusting for all risk factors (significant and non-significant) did not have an effect on the magnitude of the estimates
Table 5.4: Multivariable conditional logistic regression model, stratified by nephrotoxic medication prior to ICU admission, adjusted for matching strategy and underlying risk factors for AKI\(^a\) (OR, 95% CI)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nephrotoxic medication during hospital admission prior to ICU admission (n=296)</th>
<th>No nephrotoxic medication during hospital admission prior to ICU admission (n=1088)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>4.14 (0.97 – 17.69)</td>
<td>7.66 (1.39 – 42.16)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>3.35 (1.34 – 8.38)</td>
<td>1.96 (1.39 – 2.78)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2.03 (1.04 – 3.96)</td>
<td>1.71 (1.18 – 2.49)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>1.28 (0.20 – 8.21)</td>
<td>1.13 (0.73 – 1.74)</td>
</tr>
<tr>
<td>Captopril</td>
<td>1.06 (0.39 – 2.92)</td>
<td>1.53 (0.79 – 2.99)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>1.39 (0.39 – 4.92)</td>
<td>0.49 (0.02 – 15.45)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.93 (0.38 – 2.28)</td>
<td>0.91 (0.60 – 1.37)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.58 (0.14 – 2.44)</td>
<td>0.50 (0.12 – 2.13)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.28 (0.68 – 2.41)</td>
<td>0.95 (0.64 – 1.40)</td>
</tr>
<tr>
<td>Other nephrotoxic medications(^b)</td>
<td>1.37 (0.71 – 2.67)</td>
<td>1.30 (0.81 – 2.08)</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for: admission type, circulatory admission diagnosis, in-ICU neurological dysfunction, in-ICU respiratory dysfunction, intravenous radiologic contrast

\(^b\) Includes: acyclovir, amikacin, amphotericin, carboplatin, cidofovir, cisplatinum, cyclosporine, enalapril, enalaprilat, ethacrynic acid, flucytosine, foscarnet, hydrochlorothiazide, ifosfamide, indomethacin, methotrexate, penicillin, ramipril, sirolimus, tobramycin

5.5 Discussion

We conducted a nested case-control study to assess the association between nephrotoxic medication exposure and the development of AKI in critically ill children. To the best of our knowledge, this is the first study to do so in this patient population. We found a high nephrotoxic medication exposure rate with 80% of the study sample being exposed to one or more nephrotoxic medications during the observation period. A similar rate of nephrotoxic medication use was reported in a study of non-critically ill children (Moffett & Goldstein, 2011), suggesting that use of nephrotoxic drugs is common among both critically ill and non-critically ill hospitalized children.
We found that patients who developed AKI had an increased odds of exposure to at least one nephrotoxic medication compared to patients without AKI. However, few individual medications had a statistically significant association with the development of AKI. Many of the medications defined as nephrotoxic for the purposes of this study have a low reported incidence of nephrotoxic side effects but were included due to the lack of paediatric data. Despite this, our study has captured significant nephrotoxic effects of medications with a variety of therapeutic uses and administration frequencies in our critically ill patient population. Those effects were still significant after adjusting for differences in underlying risk factors of AKI. Interestingly, after adjustment the effect of ganciclovir increased by a factor of 1.5 (unadjusted OR=2.8, adjusted OR=4.2); in the case of ketorolac, the association became non-significant after adjustment.

Ganciclovir is known to have nephrotoxic effects; it is insoluble in human urine and precipitates in the renal tubules causing tubular obstructions (Naughton, 2008). We found ganciclovir to have the largest nephrotoxic effect (adjusted OR=4.2), though it was infrequently administered. This relative infrequency of use is likely due to institutional practice; the use of ganciclovir is restricted at our institution and there are alternative therapies available. Gentamicin, administered to approximately 21% of the study patients, was associated with the development of AKI (adjusted OR=1.73). While aminoglycoside antibacterial agents such as gentamicin are known to have nephrotoxic side effects (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012), they are used as a cost-effective, first-line treatment due to their efficacy against Gram-negative bacteria (Rea & Capitano, 2007). Recent guidelines suggest that aminoglycosides should only be used in cases where no suitable therapeutic alternatives are available (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012).
Drugs with similar efficacy, such as amikacin, are thought to also have nephrotoxic effects \((\textit{Compendium of Pharmaceuticals and Specialties 2013, 2012}; \text{ Taketomo et al., 2012})\); unfortunately, non-nephrotoxic alternatives are less effective, broad-spectrum antibiotics.

Furosemide was also found to have significant nephrotoxic effects (adjusted OR=1.9). While its use as a diuretic is important to note as a treatment of AKI, the administration of furosemide (and all other drugs) in this study occurred prior to the first sign of AKI, which was conservatively defined as a RIFLE severity of ‘Risk’. As such, it is unlikely that effect of furosemide in this study was linked to AKI treatment. Recent guidelines have suggested that diuretics should not be used to prevent or treat AKI, except for the management of fluid overload (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012).

### 5.5.1 Strengths and Limitations

This study utilized a nested case-control design which combines the advantages of both cohort and case-control studies (Szklo, 2006) and the use of incidence sampling in this study design is equivalent to matching cases and controls on the duration of follow-up (Szklo, 2006). However, there are some limitations to our study. First, our case definition was based on the RIFLE (Bellomo et al., 2004) criteria rather than the suggested pediatric modification, pRIFLE (Akcan-Arikan et al., 2007), which requires the calculation of estimated creatinine clearance (Schwartz, Brion, & Spitzer, 1987). We were unable to calculate estimated creatinine clearance as the data sources we used did not capture height. In addition, we were unable to reconcile medications from other institutions, nor did we have access to medical records from other institutions. As such, we were unable to assess the exposure to nephrotoxic medications for patients who were not admitted to our institution prior to their
ICU admission; we expect that the subgroup of patients deemed to have ‘unknown’ exposure to be a combination of patients both with and without previous nephrotoxic drug exposure. Accordingly, this group was excluded from the stratified analysis. In addition, the use of a binary exposure for medication exposure may simplify the association between drug exposure and nephrotoxicity; however, an evaluation of the drug-dose response for each medication was beyond the scope of this work. Further studies should incorporate a measure of dosage, either in total dose per kilogram or days of medication exposure. Due to small sample sizes, we did not evaluate interactions or drug synergies between medications, which have been reported to be statistically significant in other studies (Moffett & Goldstein, 2011). It may be that for some drugs, exposure to the individual medication is not as harmful as in combination with other nephrotoxic drug exposures. It should be noted that a non-significant nephrotoxic effect in our study does not necessarily indicate that the drug has no nephrotoxic effect. The infrequent use of some of the medications may have affected the power of our analyses to detect a significant effect. Furthermore, the study period was limited to the ICU setting and, as such, we may not have had adequate follow-up time for the effects of certain medications to be observed, especially those that may require longer use before AKI symptoms are evident.

5.6 Conclusions

This is the first study to assess the association between nephrotoxic medication exposure and the development of AKI in critically ill children. We found significant nephrotoxic effects of drugs in our critically ill patient population; these effects were still significant after adjusting
for differences in underlying risk factors of AKI. Nephrotoxic medication exposure was common among critically ill children, suggesting that alternative therapies should be considered to reduce the burden of nephrotoxicity in this high-risk population.
Chapter 6  General Discussion
6.1 Overview

The aim of this dissertation was to contribute new insights to the area of acute kidney injury and nephrotoxic medication exposure in critically ill children. Specifically, the goal of this thesis project was to evaluate the contribution of drug therapy to the development of acute kidney injury (AKI), a common adverse event in critically ill children. In order to accomplish this goal, we first needed to understand how AKI is defined and operationalized in the literature, and chose to focus on a specific definition of AKI known as the RIFLE. We then needed to quantify characteristics and clinical factors that place patients at higher risk for developing AKI. Finally, combining these results, we evaluated the association between specific medications and the development of AKI, controlling for underlying differences in risk. The specific objectives of this thesis work were as follows:

1. Systematically evaluate the published literature describing the use of the RIFLE definition of acute kidney injury in children

2. Determine the clinical risk factors of acute kidney injury in critically ill children

3. Evaluate the contribution of drug therapy to the development of acute kidney injury.

This chapter will present a summary of the findings for each of the above objectives. In addition, the strengths and limitations of the dissertation will be presented and the implications and future directions of the work will also be discussed.
6.2 Summary of Major Findings

6.2.1 Summary by Thesis Objectives

A summary of the major findings of this work are presented below, according to the thesis objectives.

6.2.1.1 Systematic Review of the Use of RIFLE Definition of AKI

In Chapter 3, we systematically evaluated the published literature describing the use of the RIFLE definition of acute kidney injury in children. We found that the methods used to diagnose and assess the severity of AKI were incompletely described, with few studies providing sufficient detail to confirm that the application of the RIFLE was consistent with the cited methodology. The application of the individual criteria of the RIFLE varied significantly between studies, including exclusion of the urine output criteria and differences in the operationalization of the GFR criteria, baseline GFR definitions, and methods for estimating missing baseline values. Our findings suggest that paediatric populations may be vulnerable to the same measurement-induced variability that has been reported in adult populations (Ricci et al., 2008). Furthermore, unlike adult studies (Ricci et al., 2008), our systematic review demonstrated inconsistent relationships between the RIFLE classification and measures of mortality and morbidity in children. We found discordant relationships between increasing RIFLE severity and mortality, length of stay, illness severity and other measures of kidney function.

Overall, the results of this systematic review suggest that the use of the RIFLE to assess AKI in children supports the concept of a standardized measure of acute kidney injury in children.
However, inconsistencies in the use of the RIFLE have not facilitated the comparison of rates and outcomes of AKI in this patient population. The measurement and operational issues raised by this work are relevant to newer definitions of AKI, including the AKIN (R. L. Mehta et al., 2007) and KDIGO (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) definitions of AKI.

6.2.1.2 Determining the Clinical Risk Factors of AKI

In the second study of this thesis work (Chapter 4), we evaluated a large cohort of critically ill children to determine the clinical risk factors of acute kidney injury in this patient population. We found that AKI was a common event in the paediatric ICU, occurring in nearly one-quarter of critically ill children. Our results reinforced the clinical relevance of AKI in this patient population as AKI was associated with an increased ICU length of stay and mortality rate.

Twelve independent risk factors of AKI were identified: seven were evident prior to ICU admission, including age, unplanned admission to the ICU, admission type, admission diagnoses of circulatory or respiratory disease, illness severity, and administration of a nephrotoxic medication prior to ICU admission. The five risk factors manifesting during ICU admission were markers of disease severity (neurologic or respiratory organ dysfunction) or therapeutic intervention (intravenous contrast, ECMO, nephrotoxic medication). The single greatest risk factor of ICU-acquired AKI was the in-ICU administration of nephrotoxic medication(s), underscoring the importance of furthering the limited information available regarding drug safety in paediatric populations. We found that administration of radiologic contrast was associated with lower rates of AKI, which adds to the growing evidence supporting the lack of association between AKI and contrast use.
(Brasch, 2008; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; McDonald et al., 2013; Seeliger et al., 2012; Waybill & Waybill, 2001).

6.2.1.3 Evaluation of the Contribution of Drug Therapy to Acute Kidney Injury

In the third study of this dissertation (Chapter 5), we evaluated the contribution of nephrotoxic medications to the development of acute kidney injury in critically ill children using a nested case-control study design. Our results showed that nephrotoxic medication exposure was common, with over 80% of the study population being exposed to one or more nephrotoxic medications during the study period. Patients who developed AKI had an increased odds of exposure to at least one nephrotoxic medication as compared to those patients without AKI.

We found significant nephrotoxic effects of medications with a variety of therapeutic uses and administration frequencies in the population of critically ill children studied. These effects remained significant after adjusting for differences in underlying risk factors of AKI. The administration of ganciclovir, furosemide and gentamicin was significantly associated with an increased risk of AKI. Other medications, including ketorolac, captopril, cyclosporine, and vancomycin were also associated with an increased risk of AKI, though the results were not statistically significant.

6.2.2 Five Main Findings

Overall, we identified wide variation in the application of a consensus definition of AKI, the RIFLE. We found a relatively high incidence of AKI (23.7%) among our critically ill paediatric patient population. After identifying paediatric patients at increased risk of AKI,
we found that nephrotoxic medication administration during a patient’s ICU admission was the single greatest risk factor of AKI. In addition, we found a high incidence of exposure to nephrotoxic medications with over 80% of patients exposed to one or more nephrotoxic medications. This suggests that nephrotoxic medication use should be targeted as a means to reduce the burden of AKI in this patient population.

There are five major findings from the dissertation work as a whole. These findings will be used to frame the discussion regarding implications and future directions presented later in this chapter. The main findings are:

1. Pharmacoepidemiologic methods are feasible to study adverse drug events in children

2. Acute kidney injury is common in critically ill children

3. Definitions of acute kidney injury are used inconsistently

4. Critically ill children who are at high risk for acute kidney injury can be identified

5. Nephrotoxicity is an important contributor to acute kidney injury in critically ill children.
6.3 Strengths and Limitations

6.3.1 Strengths

This dissertation has several strengths, namely the large cohort and comprehensive data available for analysis, our methodologic approach, and the definition of AKI used as the outcome measure.

6.3.1.1 Data Sources

Our quantitative analyses were based on a large cohort of critically ill children admitted to the ICU at The Hospital for Sick Children over a 42-month period. To the best of our knowledge, this is the largest cohort of critically ill paediatric patients evaluated for AKI to date. Evaluation of this large patient cohort available for study was feasible due to our use of electronic patient data. Clinical data for patients admitted to the intensive care unit at The Hospital for Sick Children are documented electronically, including demographics, clinical history, recorded vital signs and laboratory results that are documented during the patient’s stay. Using the patient’s unique medical record number (MRN), we were able to link these data to data from other clinical databases of radiology procedures, microbiology results, ICD-coded admission diagnoses, and creatinine values and medication administrations prior to ICU admission.

6.3.1.2 Methodologic Approach

Due to the large sample available, we were able to assess a large number of potential risk factors of AKI, some evident prior to ICU admission and others occurring during the ICU stay. As a number of clinical risk factors of interest were correlated, we addressed the issues
of collinearity within our data, excluding variables from the multivariable model and strengthening our analysis. The use of multivariable modeling (Chapters 4 and 5) allowed us to assess clinical factors affecting AKI as a whole rather than independently; as such we were able to model clinical reality more accurately as disease processes and treatments do not occur in isolation.

Our use of a nested case-control study design (Chapter 5) allowed us to combine the advantages of both cohort and case-control studies (Szklo, 2006). In addition, the use of incidence sampling in this study design is equivalent to matching cases and controls on the duration of follow-up (Szklo, 2006). We studied the nephrotoxic effects of a number of medications on the risk of AKI, rather than focusing on just one medication. Finally, we adjusted our estimates of risk to account for differences in underlying risk factors of AKI.

As safety data describing adverse events is limited for paediatric populations (Gilman & Gal, 1992; Uppal et al., 2008), we combined information in drug monographs with clinical expert opinions. We included a variety of specialties in the expert panel, which included a paediatric intensivist, a paediatric pharmacologist and paediatric pharmacists. Studies have shown that panel composition influences ratings, varying across specialties and between mixed and single-specialty panels (Campbell, Hann, Roland, Quayle, & Shekelle, 1999; Coulter, Adams, & Shekelle, 1995; Kahan et al., 1996; Leape, Park, Kahan, & Brook, 1992). It is suggested that expert panels should reflect the full range of stakeholders who have an interest in the study results (Boulkedid, Abdoul, Loustau, Sibony, & Alberti, 2011). Heterogeneity amongst panel members also enriches the Delphi process, as different panel members bring varying points of view regarding the quality of patient care (Hong et al., 2010).
We also evaluated the clinical use of medications rather than looking at dosage, error or appropriate dosing or prescribing. Defining an ‘appropriate’ dose is complex, especially in critically ill patients given the complexity of their disease and varying degrees of organ dysfunction. The use of a binary measure of medication administration was used as a pragmatic representation of therapeutic intent.

6.3.1.3 Definition of AKI

We used an accepted and widely used measure, the RIFLE, for our outcome of acute kidney injury, allowing for comparison of our results to other studies and patient populations. At the time of the thesis work, the RIFLE had been widely used in both adult (Ricci et al., 2008) and paediatric (M. B. Slater et al., 2012) studies. In addition, we conducted a systematic review of the existing literature regarding the use of the RIFLE to define AKI in children, allowing us to apply the lessons learned from our systematic review to our outcome definition and study methodology for our quantitative analyses. We also demonstrated the feasibility of using electronic patient data to assess AKI using the RIFLE criteria. We suggest that these results can be generalized to other, more recently proposed, measures of AKI such as the AKIN and KDIGO definitions given the modest differences between the RIFLE and these newer definitions.

6.3.2 Limitations

While this thesis work has a number of strengths, there are also some limitations that should be noted. Firstly, we studied critically ill children who were admitted to a paediatric, academic, tertiary care hospital. As such, our results may not be generalizable to nonacademic hospitals in which most children receive care. However, acutely ill children are
likely to be transferred to an academic centre, thus our results are likely generalizable to critically ill paediatric patient populations. Other limitations regarding data sources, the operationalization of nephrotoxic medications, the definition of AKI used for the outcome measure and issues related to the study period are discussed in detail below.

6.3.2.1 Data Sources

Although this work benefitted from the use of electronic patient data from a large cohort, there are also some limitations as a result of using these data. Some clinical factors thought to be associated with AKI, such as cardiac arrest and duration of cardiac bypass (Aydin et al., 2012; Fadel et al., 2012; Li et al., 2011; Rosner & Okusa, 2006), are not collected within the electronic charting systems and thus were not incorporated in our analyses. In addition, our data sources did not include medication reconciliation from other institutions. As such, we were only able to assess nephrotoxic drug exposure during the same hospital admission prior to ICU admission. Medications administered in other hospitals or at home could not be captured. It is also important to note that the data sources used for the analytic work also affected our definition of AKI; the pediatric modification of the RIFLE (Akcan-Arikan et al., 2007) is based on the calculation of estimated creatinine clearance, which requires patient height, a field which is not routinely captured in our electronic data sources.

Some risk factors had similar definitions and thus the data were highly correlated (e.g., systemic inflammatory response syndrome (SIRS) and sepsis, shock and cardiovascular dysfunction, mechanical ventilation and respiratory dysfunction). As a result, some variables were excluded from further analysis on the basis of multicollinearity. The exclusion of unmeasured and collinear variables from multivariable analyses may limit the comparability of our results to other studies. For example, while we chose to include respiratory
dysfunction over mechanical ventilation in our multivariable modeling, others may not have made the same decision.

6.3.2.2 Medications

We compiled a list of potentially nephrotoxic medications for our analysis. The list was compiled based on adverse reactions noted in drug monographs and in consultation with clinical experts; however, we may have excluded potentially relevant medications. As drug safety data is limited in children, it is possible that there are medications with unknown nephrotoxic effects in this patient population that were excluded from analysis. We should also note that some medications that were identified as being nephrotoxic, either through information in drug monographs or based on clinical expertise, were not found to have a significant nephrotoxic effect. However, it should be noted that a non-significant effect (i.e. an odds ratio with a confidence interval that includes 1.0, the null hypothesis) is very different from a result indicating that a drug is not nephrotoxic (or ‘safe’).

The use of a binary measure of medication exposure may have oversimplified the association between drug exposure and nephrotoxicity. However, an evaluation of the drug-dose response for each medication of interest was beyond the scope of this dissertation as we were interested in the clinical use of medications, a so-called “intent-to-treat” analysis.

Interactions or drug synergies between medications, which have been found to be significant in other studies (Moffett & Goldstein, 2011), were not assessed. In some drugs, exposure to the individual medication may not be as harmful as is combination with other nephrotoxic drug exposures. In addition, the infrequent use of some medications may have affected the power of our analysis to detect a significant effect.
6.3.2.3 Definition of AKI

As previously discussed (Chapter 2), the RIFLE definition of AKI was chosen to define AKI for this thesis. While other definitions of AKI are available, the RIFLE was chosen for a number of reasons. First, both the KDIGO definition and the concept of renal angina were published after the majority of the thesis work was completed. At the time of the initial planning of the study methodology, the RIFLE was widely used in both adult (Ricci et al., 2008) and paediatric studies (M. B. Slater et al., 2012). While the AKIN definition (R. L. Mehta et al., 2007) had recently been introduced, studies showed that both definitions were concordant when applied to critically ill patients (Bagshaw et al., 2008; Lopes et al., 2008) and that the AKIN did not improve mortality prediction over the RIFLE (Bagshaw et al., 2008; Chang et al., 2010). A modification of the RIFLE for use in paediatric populations (known as the pRIFLE (Akcan-Arikan et al., 2007)) had been introduced however limited justification was provided for the changes made from the original RIFLE (Akcan-Arikan et al., 2007). For example, modification of the urine output assessment from a 6-hour to an 8-hour interval may be illustrative of pragmatic customization of the RIFLE due to institutional practice or difficulty with measurement accuracy. As such, we felt the use of the RIFLE over the pRIFLE was justified.

The RIFLE and other definitions of AKI can be used to define a binary measure of acute kidney injury, as used in this thesis, as well as a measure of the severity of the injury (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). While understanding factors that affect changes, either improvement or decline, in kidney function, we felt it prudent to attempt the proposed pharmacoepidemiologic analysis with a simpler, dichotomous outcome measure before exploring more complex analyses (i.e.
longitudinal analyses with a continuous and/or dynamic outcome measure). The cut-off to define AKI was the lowest severity level of the RIFLE (‘Risk’). While some may argue that this results in a more liberal estimate of AKI incidence, research has shown that even small changes in serum creatinine are associated with adverse clinical outcomes (Coca et al., 2007; Eric A. J. Hoste et al., 2006; Lassnigg et al., 2004; Nash et al., 2002; Ostermann & Chang, 2007; Shigehiko Uchino et al., 2006) and thus any level of harm to the kidney is important to capture. The use of this cut-off coincides with the new KDIGO definition of AKI whereby a patient reaching any severity level or stage of AKI is considered to have AKI (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012).

6.3.2.3.1 Incidence of AKI Using the KDIGO Definition

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) group proposed a new definition and severity classification for AKI. It incorporates previous classifications (RIFLE, pRIFLE and AKIN) and is the first consensus definition where all elements are applicable to both paediatric and adult populations (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). The major change from previous definitions is the incorporation of a serum creatinine increase of 0.3 mg/dl within 48 hours to the definition of AKI. While definition was published after the thesis work was completed, we were interested in understanding how this change in AKI definition affected the estimated incidence of AKI in our patient population.

As previously reported (Chapter 4), according to the RIFLE definition of AKI, 915 patients (23.7%) developed AKI during their ICU admission. Based on the KDIGO definition, the estimated incidence of AKI is 24.0%, with a total of 929 patients classified as developing AKI in the ICU. Overall, a total of 117 patients met the new criteria, having a serum
creatinine increase of 0.3 mg/dl. However, the majority of these patients (88%) also met the existing criteria of a relative increase in creatinine. Only 14 patients captured by the KDIGO definition were excluded in the RIFLE definition. Thus, it appears that the addition of a serum creatinine increase of 0.3 mg/dl does not significantly change the estimated incidence of AKI.

Little evidence exists in the literature surrounding the benefit of the KDIGO criteria over other consensus definitions. A study of various AKI definitions in patients admitted with heart failure reported an AKI incidence of 36.7% based on KDIGO versus 25.6% and 27.9% according to the RIFLE and AKIN, respectively (Roy et al., 2013). During the first 7 days of hospitalization for adult patients with acute myocardial infarction (AMI), the incidence of AKI was 14.8% and 36.6% according to the RIFLE and KDIGO definitions (Rodrigues et al., 2013). Patients undergoing cardiac surgery had post-surgical AKI rates of 25.9% according to either the AKIN or KDIGO and 24.9% based on the RIFLE (Bastin et al., 2013). All studies were performed in adult patient populations and used only the serum creatinine criteria of the definitions.

6.3.2.4 Study Period

The study period for all quantitative analyses in this thesis was the patient’s ICU admission. One concern with the study period being limited to a patient’s ICU stay is that this approach overlooks AKI that presents after ICU discharge. We initially considered following patients from the time they were admitted to the ICU until they were discharged from the hospital. However, clinical practice varies between the ICU and the hospital wards. For example, vital signs are collected more frequently in the ICU. Creatinine is not part of routine clinical assessment in the ward and thus is only measured or monitored in patients who are judged to
be at risk of kidney injury. In addition, urine output is not consistently documented in patients on the ward. Given the discrepancies in data availability between the ICU and hospital ward, the study period was limited to the ICU setting and, as such, we may not have had significant follow-up time for the effects of certain medications to be observed, especially those that may require longer use before AKI symptoms are evident. The issue of timing may also explain our findings related to contrast use: serum creatinine levels have been shown to peak three days after contrast administration (Marenzi et al., 2004; Solomon, 1998) and, as such, the effects of contrast use may not be apparent until after ICU discharge (i.e. after the period of ‘critical illness’ associated with ICU admission).

6.4 Implications and Future Directions

6.4.1 Implications

This dissertation has added to the literature regarding the incidence of acute kidney injury in critically ill children and helps to shed light on the importance and scope of AKI in this patient population. The intent for this section is to focus on the clinical and research implications of the main findings of the thesis work.

6.4.1.1 Pharmacoepidemiologic Methods Are Feasible

Overall, our work illustrates that a pharmacoepidemiologic approach can be utilized to quantify and study adverse drug events in paediatric patients, a generally understudied patient population. Given the small sample sizes available for studies of paediatric patients and the limited availability of administrative pharmacological data sources for paediatric populations
(i.e. for adults over the age of 65, all prescriptions are available through the Ontario Drug Benefit claims database), using hospital data systems as sources of drug safety may address a significant gap in drug safety research. This approach can be utilized as a method to study other adverse drug events in this population or other small patient populations.

6.4.1.2 AKI Is Common In Critically Ill Children

In our large cohort of critically ill children, we found that AKI was a relatively common occurrence, with roughly one-quarter of critically ill children developing some degree of renal injury during their ICU admission. This is as common as other types of organ failure (Devarajan, 2013) and clinicians should be aware of the risk of AKI in critically ill children. Despite our findings, AKI appears to be underappreciated by clinicians and researchers and is not recognized by the public (Kellum, Bellomo, & Ronco, 2012). Placing AKI in the perspective of other well-publicized diseases, AKI has an estimated incidence similar to that of acute myocardial infarction, a condition widely recognized by clinicians, researchers and the public (Ali et al., 2007). Strategies are needed to increase awareness of AKI and its implications amongst all groups.

6.4.1.3 AKI Definitions Are Used Inconsistently

The field of AKI continues to evolve. With the publication of the RIFLE in 2004, four consensus definitions of AKI have been released over an 8-year period. The most recent consensus definition, the KDIGO, which incorporates earlier AKI classifications (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012), appears to be the new, accepted definition of AKI. While an accurate definition of AKI is important, ever-changing guidelines make it difficult for clinicians and researchers to ensure
they are using the most recent definition. Our post-hoc evaluation of the newly proposed KDIGO criteria illustrated minimal impact of the revised criteria on patients identified as having AKI, questioning the value of this new refinement. Little evidence exists in the literature surrounding the benefit of the KDIGO criteria over other consensus definitions and available data are conflicting (Bastin et al., 2013; Rodrigues et al., 2013; Roy et al., 2013).

Given the inconsistent application of explicitly defined criteria such as the RIFLE, work should be focused on appropriate usage of existing definitions and improving consistency in reporting to improve transparency and comparability of study results. Consistent application of any consensus definition is crucial to provide valid estimates of AKI (Siew et al., 2010; Zavada et al., 2010) and allow meaningful comparisons across study populations to evaluate treatments and outcomes of AKI. Any modifications to a standardized outcome definition such as the RIFLE (Bellomo et al., 2004) or the new KDIGO definition (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) reduces the utility of a consensus definition of AKI.

The importance of this issue becomes more relevant when we consider that these standard definitions are being used as outcome measures in studies evaluating the effectiveness of treatments and other interventions and are being used as the “gold standard” comparison for the development of new biomarkers to improve the timeliness of AKI diagnosis. In order for clinicians and researchers to make appropriate evidence-based decisions, we must ensure that the data being analyzed are valid and consistent. Recognizing that pragmatic decisions are being made when these definitions are applied in epidemiologic studies, consistency and transparency are important. A number of studies will mention the use of the RIFLE or other consensus definition in their methodology but will make modifications to the definition,
potentially excluding either of the GFR or urine output criteria. Consensus panels should provide clear directions for how to appropriately use and reference these methodologies including outlining what modifications or exclusions, if any, are permissible. This will help to improve the transparency and consistency of the definition of AKI in the literature similar to the reporting of randomized trials via the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher, Schulz, & Altman, 2001) or the PRISMA statement for reporting systematic reviews and meta-analyses (Liberati et al., 2009).

6.4.1.4 Critically Ill Children at Risk for AKI Can Be Identified

Understanding the factors that place children at higher risk of developing AKI will allow clinicians to prospectively profile patients and adjust therapeutic decisions based on the patient’s risk of kidney injury. Clinicians need to be able to prospectively disentangle drug and disease effects on the kidneys in individual patients to appropriately target therapeutic interventions and avoid high-risk treatments in patients who are more susceptible to AKI. In certain circumstances, it may be impossible to avoid certain treatments or factors that may damage kidneys (i.e. no ‘safer’ alternatives exist for a needed therapy) but co-interventions can be selected to mitigate the negative effects of these treatments.

Our analysis of the risk factors of AKI revealed two important findings: trauma and radiologic contrast were not associated with subsequent development of AKI. Trauma has been previously reported as a risk factor of AKI in both adults (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; Shigehiko Uchino et al., 2006) and children (Wohlauer et al., 2012); however, Bailey et al (Bailey et al., 2007) and Plotz et al (F. B. Plotz et al., 2005) found the association between AKI and an admission diagnosis of trauma to be statistically non-significant in critically ill children. These studies
involved smaller sample sizes and may have been underpowered to detect a statistically significant difference. More importantly, we found that radiologic contrast administration was associated with lower rates of AKI. Previous literature has reported contrast administration as a risk factor of AKI (Brasch, 2008; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; Seeliger et al., 2012; Waybill & Waybill, 2001); however, the association between contrast administration and AKI has recently been questioned (McDonald et al., 2013). While more work is needed to elucidate the causal relationships between trauma and contrast administration and the development of kidney injury, it may be that the factors that were thought to predispose patients to AKI may have changed (for example, trauma management, patient selection for contrast, and contrast agents themselves) and there may be a corresponding need to educate clinicians as to the changing landscape of AKI.

6.4.1.5 Nephrotoxicity Is an Important Contributor to AKI in Critically Ill Children

We found that the single greatest risk factor of ICU-acquired AKI was the administration of nephrotoxic medications, indicating that scrutiny of the drugs used in the paediatric ICU setting is warranted. Our results reinforce the high level of nephrotoxicity associated with furosemide, ganciclovir and gentamicin. While other drugs also showed non-significant associations with the development of AKI, including captopril, cyclosporine, ketorolac and vancomycin, it should be noted that a non-significant nephrotoxic effect in our study results does not necessarily indicate that the drug has no nephrotoxic effect. A lack of association between a potentially nephrotoxic drug and AKI in our study does not guarantee that the medication is safe or has no nephrotoxic effects given some of the limitations mentioned earlier within this chapter. Our work has illustrated the need for more work to understand the
nephrotoxic potential of medications in paediatric populations as safety data from adult populations may not be applicable.

Our findings have implications on prescribing practices: lessons from contrast guidelines (Benko et al., 2007; Solomon & Deray, 2006; Stacul et al., 2011) and recent recommendations for aminoglycoside and amphotericin-induced AKI prevention (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) should be applied to all potential nephrotoxic drugs: nephrotoxic medications should be used only where clinically sensible alternatives do not exist for all patients, especially those identified to be at high-risk.

6.4.2 Future Directions

This section describes the potential future directions for this body of research. Here the most important new questions that arose from this dissertation are described and means to address them are proposed.

6.4.2.1 Expand Pharmacoepidemiologic Approach

This work has demonstrated the feasibility of a pharmacoepidemiologic approach to evaluate adverse drug events in critically ill children. The specific approach used to study acute kidney injury should be expanded in a number of ways. Firstly, our analysis dealt with a simple, binary outcome of acute kidney injury. Further work should expand this outcome definition to incorporate disease severity; there may be certain clinical factors or medications that are associated with milder or more severe forms of renal injury.
Second, future work could incorporate the reversibility of kidney injury. Roughly 80% of children with hospital-acquired AKI either fully recover or have improved renal function by hospital discharge (Hui-Stickle et al., 2005) and a recent study of vancomycin-induced AKI in critically ill children found that the renal injury was resolved in 87% of patients (Totapally et al., 2013). Incorporating the reversibility of AKI would allow us to not only understand factors associated with the development of AKI but also factors that affect renal recovery. This analysis may help develop potential therapies for AKI and assist clinicians in providing better care and improve outcomes for patients.

Third, the focus of this work was limited to the ICU environment; future studies should look at post-ICU kidney injury and long-term renal function. This will also allow an expansion of the definition of AKI to include the full spectrum of severity according to the RIFLE criteria; this dissertation did not include severity levels of ‘Loss’ and ‘End-stage’ which are defined by long-term use of renal replacement therapy (>4 weeks) and not applicable given that most patients are discharged from the ICU within 2 days. Interestingly, newer definitions of AKI, including the AKIN and KDIGO, do not include renal replacement therapy in their definitions.

Fourth, enhanced description of the exposure of interest may allow for a more detailed understanding of nephrotoxicity as a dose-dependent phenomenon. In this work, we considered drug administration as a binary measure; future work should incorporate drug dosage or length of drug exposure (Moffett & Goldstein, 2011). For drugs monitored for therapeutic efficacy (i.e. vancomycin), peak and trough concentrations may be studied. For example, while a recent study of vancomycin-induced AKI in critically ill children did not find a significant relationship between the development of AKI and total vancomycin dose
and peak or trough levels (Totapally et al., 2013), high vancomycin trough concentrations have been shown to be associated with an increased risk of nephrotoxicity (Elting et al., 1998; Hermsen et al., 2010; Hidayat, Hsu, Quist, Shriner, & Wong-Beringer, 2006; Lodise, Patel, Lomaestro, Rodvold, & Drusano, 2009; McKamy et al., 2011; Pritchard et al., 2010).

We considered 29 medications to have potential nephrotoxic effects and included these drugs in our analyses. However, given the limited knowledge of drug safety in children, it is possible that we may have excluded relevant medications. Future work should broaden the scope of medications used in these analyses or limit a priori assumptions of toxicity of medications. The role of drug-drug and drug-disease interactions should also be assessed in future studies. For some drugs, exposure to the individual medication may not be as harmful as when these therapies are combined with other nephrotoxic exposures; drug interactions have been reported as having significant associations with nephrotoxicity in other studies (Moffett & Goldstein, 2011).

The recent changes to the consensus definition have incorporated a rise in creatinine of 0.3 mg/dl SCr within 48 hours, which is applicable to pediatric patients (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). We have shown that this new definition does not significantly alter the estimated incidence of AKI, however, the quantitative analyses presented here should be rerun to confirm that this change in definition does not alter the associations described in this dissertation. Finally, in addition to expanding the scope of the evaluation of AKI, the approach taken with this adverse drug event could be utilized to study hepatotoxicity, electrolyte or metabolic disturbances or other adverse events.
6.4.2.2 Improve Consistency in the Use of AKI Definitions

Any modifications to a standardized outcome definition such as the RIFLE (Bellomo et al., 2004) or the new KDIGO definition (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) reduces the effectiveness of a consensus definition of AKI. Further work is needed to understand the impact of the KDIGO criteria on the estimated incidence of AKI relative to existing definitions; currently little work has been done in this area and the results are conflicting (Bastin et al., 2013; Rodrigues et al., 2013; Roy et al., 2013).

Given the inconsistencies in the use of consensus definitions of AKI, work should be focused on appropriate usage of existing definitions and improving consistency in reporting to improve transparency and comparability of study results. One solution is the development of a framework, such as the Consolidated Standards of Reporting Trials (CONSORT) statement (Moher et al., 2001) or the PRISMA statement for reporting systematic reviews and meta-analyses (Liberati et al., 2009). Future studies should also look to the clinical relevance of changes to consensus guidelines. Do clinicians feel that the minor changes made to the existing definitions (i.e. RIFLE and AKIN) to develop the KDIGO are clinically relevant? A survey of clinicians may help expert future panels to identify clinically relevant questions and considerations during the development of consensus definitions. In addition, an analysis comparing various definitions of AKI and their relationships with clinical outcomes such as morbidity and mortality is also necessary to determine if one definition is more predictive of patient outcome than others.

Despite the changes in guidelines, the lessons learned from this thesis regarding the implementation of RIFLE are applicable to this and other outcome or disease definitions. We
found a large variation in how a consensus definition of AKI was applied. It is widely agreed that urine output has a high sensitivity and specificity to diagnose AKI (Eric A. J. Hoste & Kellum, 2006), however studies have excluded the urine output criteria from their AKI definition. If few institutions capture urine output in a usable way, is it appropriate or useful for a consensus definition to include it? With current and future research focused on the development of biomarkers a substitute measure for urine output may be found and incorporated in the next consensus definition. Perhaps rather than continually perfecting a definition that uses traditional measures of kidney function (serum creatinine and urine output), future consensus definitions should only be changed when more time-sensitive biomarkers are developed and readily available for day-to-day clinical use.

While many studies claim that the RIFLE is a validated measure of AKI in both adults (Ricci et al., 2008) and children (Akcan-Arikan et al., 2007), our work found inconsistent relationships between the RIFLE classification and measures of mortality and morbidity in children. Further work is needed to clarify these associations. However, while demonstration of correlations between the RIFLE and measures of mortality and morbidity are useful, they are not demonstrative of the RIFLE’s ability to accurately reflect acute kidney injury. Correlation with mortality is only one form of validation and, on its own, insufficient. In other words, the RIFLE may be a good measure of illness severity, but may not truly capture the presence of AKI. Future work should appropriately validate the RIFLE, or KDIGO definitions of AKI, as a true measure of kidney injury. Ideally, validation would occur with a comparison of the RIFLE with a ‘gold standard’ measure of acute kidney injury. However, unlike chronic kidney disease, no ‘gold standard’ diagnostic test exists for the diagnosis and severity classification of acute kidney injury; it is based on a combination of patient symptoms, clinical tests, and clinical judgment. Substitute measures of kidney
function have been assessed, such as the relationship between the RIFLE and renal replacement therapy (Duzova et al., 2010; Frans B. Plotz et al., 2008; Zappitelli et al., 2009). However, the value of these assessments is limited as the use of renal replacement therapy is captured within the RIFLE definition and non-renal indications for dialysis also exist. For example, renal replacement therapy can be used to treat patients with tumor lysis syndrome or drug toxicity (Fleming et al., 2012). Thus, surrogate measures of kidney function that are not captured in the RIFLE definition should be assessed. For example, one major function of the kidneys is regulation of electrolytes, abnormally low or high levels of sodium or potassium would be indicative of kidney dysfunction. Thus, one method of validating the RIFLE would be to compare RIFLE severity levels against electrolyte levels. Again, it is useful to point out that issues related to validation also are relevant to other, newer definitions of AKI, including the KDIGO (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) consensus definitions.

6.4.2.3 Improve Ability to Identify At Risk Populations

We identified a number of risk factors of AKI in critically ill children. The next step for this work is to develop and validate a prospective risk assessment or prediction model to help clinicians identify high-risk patients. This model may take the form of a risk score, such as the Pediatric Risk of Mortality (PRISM) score (Pollack et al., 1988) or the Paediatric Index of Mortality (PIM2) score (A. Slater, Shann, & Pearson, 2003), currently used in paediatric medicine, or may follow a decision tree. The goal is to develop an easy set of rules to help clinicians identify and target patients at risk for AKI. Once this work is complete, it will need to be evaluated for its effectiveness: is this information valuable to clinicians? Does it provide clinicians with a way to easily identify and target at-risk children, improve their
ability to provide appropriate and effective care and ultimately improve patient outcomes?

Ultimately, this work could be incorporated into an electronic medical record (EMR) to provide real-time decision support to clinicians.

This work has also been hypothesis-generating and has highlighted areas where more research is needed. For example, our work found radiologic contrast administration, long thought to be a risk factor for AKI (Brasch, 2008; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012; Seeliger et al., 2012; Waybill & Waybill, 2001), was associated with lower rates of AKI in our cohort of critically ill children. A recent analysis of observational studies showed that contrast administration was not associated with AKI, death or dialysis (McDonald et al., 2013). There are a number of reasons that may explain these findings (for instance, clinicians may avoid using contrast in critically ill children who they perceive are at risk for renal injury); as such, further work is needed to elucidate the causal association between contrast administration and the development of acute kidney injury in critically ill children. While there may be a number of explanations for the effect we found, if contrast is indeed nephrotoxic, clinicians may be approaching patients given contrast in a manner as to dampen the potential injury to the renal system. It is important to understand this complex process as the lessons from contrast guidelines (Benko et al., 2007; Solomon & Deray, 2006; Stacul et al., 2011) may be applied to other nephrotoxic medications to reduce their burden on the renal system. Prospective studies of clinical practice and clinical decision-making surrounding the treatment of patients who are administered contrast are needed to elucidate this complex process.
### 6.4.2.4 Improve Safety Profiles and Increase Alternative Treatments to Nephrotoxic Drugs

Given that our work has shown that nephrotoxic drugs are the primary risk factor of ICU-acquired kidney injury, investigations into the use of potential alternatives with less nephrotoxic profiles is necessary. For example, we found that gentamicin was significantly associated with the development of AKI. While aminoglycoside antibacterial agents such as gentamicin are known to have nephrotoxic side effects (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012), they are used as a cost-effective, first-line treatment due to their efficacy against Gram-negative bacteria (Rea & Capitano, 2007). Recent guidelines suggest that aminoglycosides should only be used in cases where no suitable therapeutic alternatives are available (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012). Drugs that may have similar efficacy, such as amikacin and vancomycin, are thought to also have nephrotoxic effects (Compendium of Pharmaceuticals and Specialties 2013, 2012; Taketomo et al., 2012); unfortunately, non-nephrotoxic alternatives may be less effective. This points to an obvious need to find suitable, effective and safe alternatives to medications with nephrotoxic side effects or safer methods of administration (i.e. once daily aminoglycoside dosing, continuous infusions of amphotericin B).

Our work has also highlighted a number of drugs for which there is limited empiric information regarding their nephrotoxic effects. A number of drugs, including captopril, cyclosporine, ketorolac and vancomycin, showed non-significant associations with the development of AKI in this work. In the case of vancomycin, studies have shown differing results: while high vancomycin trough concentrations have been shown to be associated with
an increased risk of nephrotoxicity (Elting et al., 1998; Hermsen et al., 2010; Hidayat et al., 2006; Lodise et al., 2009; McKamy et al., 2011; Pritchard et al., 2010), a recent study of vancomycin-induced AKI in critically ill children did not find a significant relationship between the development of AKI and total vancomycin dose and peak or trough levels (Totapally et al., 2013). Recent adult data shows vancomycin to be minimally nephrotoxic, even among high-risk, critically ill patients (Davies, Guidry, Petroze, Hranjec, & Sawyer, 2013). This highlights the need for more bench and bedside research to clearly understand the mechanisms of drug-induced kidney injury.

In addition, our work demonstrates the need for better articulation of what constitutes a nephrotoxic medication. When refining the list of potentially nephrotoxic medications for inclusion in the analytic work, our expert panel demonstrated resolvable disagreement which points to some ambiguity in the field. Our definition of nephrotoxic medications was supported by ‘overall’ assessment in our cohort study (i.e. administration of a nephrotoxic medication was associated with the development of acute kidney injury). However, when the association between individual medications and the development of AKI was studied, the assumed nephrotoxicity of many medications was not supported by our results. While these results may be due to the limitations of our work, it may be that, for some medications, the label of nephrotoxic may be historic and not well deserved. It may be that a definition of nephrotoxicity of a medication needs to not only be comprehensive in its assessment of frequency and severity, but may also need to incorporate the mechanism of injury or be applied separately to specific age groups.

Future work should include interventional studies evaluating the safety and efficacy of alternatives to nephrotoxic medications. In addition, we suggest that it would be useful to
study the effectiveness of applying the recent recommendations for aminoglycoside and amphotericin-induced AKI prevention (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Working Group, 2012) to all potentially nephrotoxic drugs. This could either be done in a randomized controlled trial, with certain patients or institutions randomized to follow the recommendations and others randomized to standard care, or in a before-after study where the standard of care is followed for a certain amount of time and then the recommendations are applied. In the latter situation, each institution would act as its own control. If feasibility prohibits these controlled study designs, a pharmacoepidemiologic approach, such as was used in this thesis, could be used to compare the effects of differing treatment approaches on the development of AKI, allowing for risk-adjustment to control for underlying differences between patients.

6.5 Summary

In summary, the current investigation has confirmed that acute kidney injury is a common event in critically ill children and that nephrotoxic medications are an important contributor to this disease. The findings from these three studies have provided important contributions to, and advanced our knowledge of, our understanding nephrotoxic medications and other risk factors of AKI. Further research should focus on methods to reduce the occurrence of acute kidney injury in critically ill children, including improving awareness of the burden of AKI and improving consistency in the use of consensus definitions of AKI. It is necessary to improve clinicians’ abilities to identify patients at risk of developing AKI and efforts are needed to provide therapeutic alternatives to medications with high nephrotoxic profiles.
Finally, the pharmacoepidemiologic approach used in this dissertation should be expanded in the study of AKI in critically ill children and could be applied to the study of other adverse drug events. The results of this and future work can help to optimize prescribing and aid clinicians in making optimal treatment choices, reducing therapeutic harm and improving patient outcomes.
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